PB84-118843

# Health Assessment Document for 1,1,2-Trichloro-1,2,2-Trifluoroethane (Chlorofluorocarbon CFC-113) Final Report

(U.S.) Environmental Protection Agency
Washington, DC

Sep 83

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

Office of Health and
Environmental Assessment
Washington DC 20460

EPA-600/8-82-002F
September 1983
Final Report

Research and Development

PB84-118643

EPA

# Health Assessment Document for 1,1,2-Trichloro-1, 2, 2-Trifluoroethane (Chlorofluorocarbon CFC-113)

Final Report

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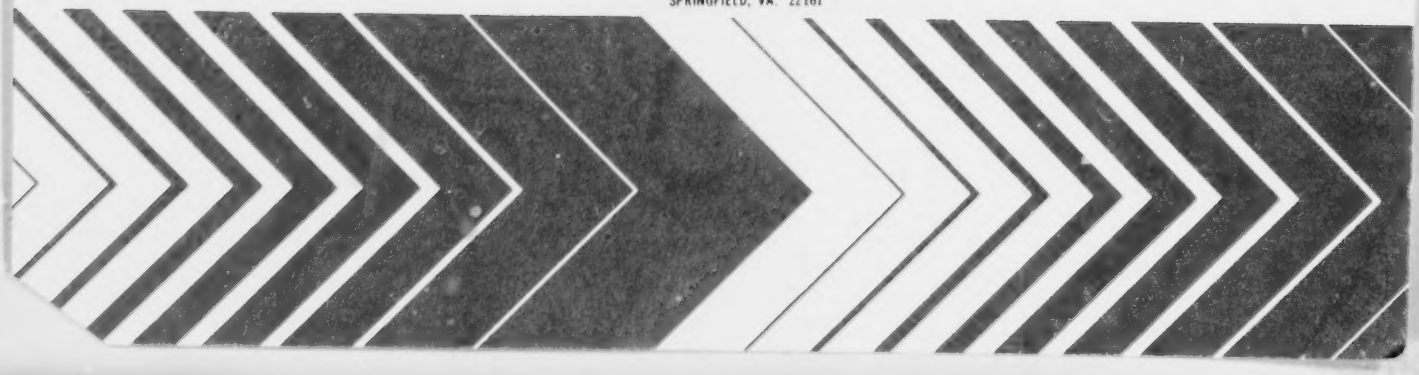

**TECHNICAL REPORT DATA**
*(Please read Instructions on the reverse before completing)*

| 1. REPORT NO. | 2. | 3. RECIPIENT'S ACCESSION NO. |
|---|---|---|
| EPA-600/8-82-002 F | | PB84 118843 |

| 4. TITLE AND SUBTITLE | 5. REPORT DATE |
|---|---|
| Health Assessment Document for 1,1,2-Trichloro-1,2,2-Trifluoroethane (Chlorofluorocarbon CFC-113)--Final Report | September 1983 |
| | 6. PERFORMING ORGANIZATION CODE |
| 7. AUTHOR(S) | 8. PERFORMING ORGANIZATION REPORT NO. |
| Richard Carchman, VA Commonwealth Univ., Mark M. Greenberg; U.S. EPA | |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS | 10. PROGRAM ELEMENT NO. |
| U.S. Environmental Protection Agency<br>Environmental Criteria and Assessment Office<br>MD-52<br>Research Triangle Park, NC 27711 | 11. CONTRACT/GRANT NO. |
| 12. SPONSORING AGENCY NAME AND ADDRESS | 13. TYPE OF REPORT AND PERIOD COVERED |
| Office of Health & Environmental Assessment<br>Office of Research and Development<br>U.S. Environmental Protection Agency<br>Washington, DC 20460 | Final |
| | 14. SPONSORING AGENCY CODE<br>EPA/600/21 |

15. SUPPLEMENTARY NOTES

16. ABSTRACT

Chlorofluorocarbon 113 (1,1,2-trichloro-1,2,2,-trifluoroethane) has little potential to cause direct adverse health effects at levels found or expected in the general environment (<4.2 ppb). Experimental data do not indicate adverse health effects in humans at a TLV of 1,000 ppm. At exposure levels greatly exceeding 1,000 ppm, impairment of neurological and cognitive functions (humans) and detrimental cardiovascular effects (animals) have been observed.

17. KEY WORDS AND DOCUMENT ANALYSIS

| a. DESCRIPTORS | b. IDENTIFIERS/OPEN ENDED TERMS | c. COSATI Field/Group |
|---|---|---|
| | | |

| 18. DISTRIBUTION STATEMENT | 19. SECURITY CLASS *(This Report)* | 21. NO. OF PAGES |
|---|---|---|
| Distribute to Public | Unclassified | 84 |
| | 20. SECURITY CLASS *(This page)* | 22. PRICE |
| | Unclassified | |

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

EPA-600/8-82-002F
September 1983
Final Report

# Health Assessment Document for 1, 1, 2-Trichloro-1, 2, 2-Trifluoroethane (Chlorofluorocarbon CFC-113)

## FINAL REPORT

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Research Triangle Park, NC 27711

NOTICE

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for presentation and publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

## PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a "source document" for EPA use. Originally the health assessment was developed for use by the Office of Air Quality Planning and Standards to support decision-making regarding possible regulation of CFC-113 as a hazardous air pollutant. However, at the request of the Agency's Work Group on Solvents the assessment scope was expanded to address multimedia aspects.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed-effect levels and dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

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## ABSTRACT

Chlorofluorocarbon-113 (CFC-113; 1,1,2-trichloro-1,2,2-trifluoroethane) is a solvent characterized by a high vapor pressure and very low solubility in water. Human exposure to CFC-113 is predominantly by inhalation. There is no evidence indicating that human health effects are likely to occur at ambient air mixing ratios (e.g. 18 parts-per-trillion or $0.14 \times 10^{-3}$ mg/m$^3$) found or expected in the general environment or even at higher levels (< 4 parts-per-billion or < 0.032 mg/m$^3$) sometimes observed in urban areas. In fact, available experimental data do not indicate that any adverse health effects are directly induced in humans at a TLV® of 1,000 ppm (7,700 mg/m$^3$) due to exposure to CFC-113.

There is presently inadequate published information to assess the carcinogenic potential of CFC-113. A two-year chronic inhalation study in rats at exposure levels of 2,000; 10,000; and 20,000 ppm has been completed. Preliminary observations are consistent with no effects attributable to CFC-113 except decreased weight gain in animals exposed to 20,000 ppm only. Similarly, limited testing has not indicated that CFC-113 is teratogenic or mutagenic. Preliminary results of a one-generation reproductive toxicity/teratogenicity study in rats suggest that, at exposure levels up to 25,000 ppm, CFC-113 does not cause teratogenesis or embryotoxic effects.

# 1. SUMMARY AND CONCLUSIONS

Compared with other halogenated hydrocarbon solvents with similar usage in industry, less information is available from the literature on chlorofluorocarbon-113 (CFC-113; 1,1,2-trichloro-1,2,2-trifluoroethane). CFC-113 is primarily of concern as a pollutant of the atmosphere. It has a high vapor pressure and is practically insoluble in water. No direct ecosystem effects of CFC-113 have been reported in the scientific literature; however, the high volatility and the absence of measurable levels in water suggest that CFC-113 poses little or no risk to aquatic species. Similarly, presently available health effects information indicates that CFC-113 poses little or no risk at presently encountered environmental concentrations in terms of the direct induction of adverse human health effects.

Human exposure to CFC-113 is predominantly by inhalation and most CFC-113 is rapidly cleared from the body by exhalation. Animal exposure studies indicate that CFC-113 partitions preferentially into lipid-rich tissues and is poorly metabolized. Loss of CFC-113 from all tissues is rapid during post-exposure periods, with virtually 100 percent clearance within 24 hours after cessation of acute exposure.

In regard to potential health effects associated with CFC-113, there is no evidence indicating that human health effects are likely to occur at ambient air mixing ratios (e.g., 18 ppt; $0.14 \times 10^{-3}$ mg/m$^3$) found or expected in the general environment or even at higher levels (<4,160 ppt; <0.032 mg/m$^3$) sometimes observed in urban areas. In fact, available experimental data do not indicate that any adverse health effects are directly induced in humans at a TLV® of 1,000 ppm (7,700 mg/m$^3$) due to exposure to CFC-113.

At exposure levels greatly exceeding 1,000 ppm (7,700 mg/m$^3$), impairment of neurological and cognitive functions (humans) and detrimental cardiovascular effects (animals) have been observed following acute exposure to CFC-113. However, because of the lack of detailed studies in these health areas, a conclusive assessment of the human health risks posed by levels of CFC-113 in the range 1,500 to 2,000 ppm (11,550 to 15,400 mg/m$^3$) cannot be made. Also, before definitive conclusions concerning the effects of chronic long-term

exposure to CFC-113 can be drawn, the results of a recently completed two-year chronic inhalation study† in rats must be evaluated. What information is available concerning health effects associated (or potentially associated) with acute or chronic exposure to CFC-113 is summarized below.

CARCINOGENICITY AND MUTAGENICITY

There is presently inadequate published information to assess the carcinogenic potential of CFC-113. A two-year chronic inhalation study in rats at exposure levels of 2,000; 10,000; and 20,000 ppm (15,400; 77,700; and 154,000 $mg/m^3$) has recently been completed at Haskell Laboratories. Histopathology is in progress. Final assessment is expected to be completed in late 1983.

Chlorofluorocarbon 113 was negative in one Ames test, with and without metabolic activation. It was also reported to be negative in a dominant lethal assay in mice. Because of limited testing performed and the insensitivity of the dominant lethal assays to detect gene mutations, further testing is needed before definitive conclusions can be drawn.

TERATOGENICITY AND REPRODUCTIVE EFFECTS

No clinical cases associate human exposure to CFC-113 with congenital malformations in children. No epidemiological studies are available. Although no published animal studies are available that adequately assess the teratogenic or adverse reproductive potential of CFC-113, unpublished data from two studies conducted for E. I. duPont de Nemours and Company indicate that CFC-113 did not produce toxic effects unique to rabbit conceptus at levels that were maternally toxic. It should be noted that these studies have inadequacies and are best considered as pilot evaluations only. Maternal and fetal death precluded evaluation of a sufficient number of litters to establish the teratogenic potential of CFC-113. Evaluation of the viable litters showed no indication of a teratogenic effect.

Preliminary results of a recently-completed one-generation teratogenicity/reproductive toxicity study in pregnant rats also suggest that at the exposure levels tested (5,000, 12,500, and 25,000 ppm) there was no evidence of teratogenic or embryotoxic effects attributable to CFC-113.

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†Preliminary observations are consistent with no effects attributable to CFC-113 except decreased weight gain in animals exposed to the highest inhalation level only. Histopathology will be completed in 1983. Exposure levels were 2,000, 10,000, and 20,000 ppm. (See Section 5.1.4 for reference.)

A definitive assessment of the potential of CFC-113 to cause adverse teratogenic or reproductive effects can only be made after data from the two-year chronic inhalation study in rats and other reproductive studies currently underway are evaluated, and additional data are generated, if needed, that are in accordance with current teratologic and reproductive testing.

NEUROLOGICAL EFFECTS

A noticeable impairment of psychophysiological function (as measured by task performance) has been reported in two humans exposed to 2,500 to 4,500 ppm (19,250 to 34,650 $mg/m^3$) of CFC-113 for 30 minutes to 1 hour. Effects disappeared within 15 minutes after cessation of exposure. No impairment of performance at exposure levels of 500 and 1,000 ppm (3,850 and 7,700 $mg/m^3$) was observed during two weeks of exposure, or at 1,500 ppm (11,550 $mg/m^3$) for 2.75 hours.

CARDIOVASCULAR EFFECTS

Serious cardiovascular effects are unreported in humans. Various animal studies (non-human primates and dogs) have indicated that acute exposure to high concentrations of CFC-113 (as low as 2,000 ppm or 15,400 $mg/m^3$ in a 6-hour exposure period) followed by a large injected dose of epinephrine resulted in cardiac arrhythmias. Concentrations as high as 20,000 ppm (154,000 $mg/m^3$), however, did not sensitize a dog's heart to its own circulating level of epinephrine even when it was elevated by exercise. The compound may spontaneously induce myocardial depression by a direct effect on cardiac muscle, decrease contractile performance, and lead to hypotension by decreasing cardiac output and directly affecting peripheral vasodilation at much higher levels (at or above 25,000 ppm or 192,500 $mg/m^3$).

HEPATOTOXICITY

Preliminary data from an industry-sponsored, two-year chronic inhalation study in rats indicate no hepatotoxic effects attributable to CFC-113 at doses as high as 20,000 ppm (154,000 $mg/m^3$).

STRATOSPHERIC POLLUTION AND OZONE DEPLETION

Chlorofluorocarbon 113 and other structurally similar compounds, are very resistant to destruction in lower portions of the atmosphere, i.e., the troposphere. Because it is essentially inert in the troposphere, CFC-113 is transported slowly to the stratosphere.

A thin shield of ozone ($O_3$) is located in the stratosphere, 10 to 50 kilometers above the Earth's surface. Because $O_3$ effectively absorbs ultraviolet-B radiation (in the wavelength range 290 to 320 nm), any actual decrease in stratospheric ozone ($O_3$) concentration is expected to result in an increased amount of this biologically-damaging radiation (incident at the earth's surface). Photochemical reactions involving a variety of substances produced by human activities, including certain halogenated organic compounds, appear to have some potential to perturb $O_3$ in the stratosphere; and if a decrease in total $O_3$ were to occur, it is hypothesized that an increased incidence in non-melanoma skin cancer might result. However, there is presently no evidence demonstrating that such an indirect effect of CFC-113 on human health has occurred or is likely to occur as the result of its entry into the atmosphere at current emission rates.

Chlorofluorocarbons have exceedingly long atmospheric lifetimes relative to most other atmospheric pollutants. CFC-113 is estimated to have a stratospheric lifetime in the range of 86 to 100 years, but it remains to be demonstrated that this results in any significant depletion of stratospheric $O_3$. It is not possible to estimate the extent to which perturbation of $O_3$ may be associated with atmospheric loadings of CFC-113. All photochemical processes that may affect $O_3$, including those involving substances other than CFCs, must be taken into account before realistic estimates of $O_3$ change due to CFC-113 or other halocarbons can be made.

RECOMMENDATIONS FOR FURTHER STUDIES

Although the available human and toxicity data indicate that ambient exposure to CFC-113 does not currently present a human health hazard, it is apparent that further investigation is needed in several areas. Areas in which incomplete information is available, and that should be considered in formulating research needs, are presented below. This is not, however, a list of research priorities.

1. Neurobehavioral toxicity. Although the effects of acute high-level exposure to CFC-113 have been documented, there is a paucity of data regarding the behavioral and neurological effects of pure CFC-113 at chronic exposure levels less than 1,000 ppm. The extent, nature, and threshold of neurobehavioral effects need to be determined to properly evaluate

potential risks from chronic ambient exposure. Epidemiological studies of exposed workers may represent a mechanism by which these data can be obtained.

2. Carcinogenicity. While the results of the ongoing, industry-sponsored bioassay may fill the data gaps, it would be desirable to have confirmation of these results, in another rodent strain, by independent bioassay. Similar results in two or more animal strains should provide the level of evidence necessary to more effectively gauge the cancer potential of CFC-113.
3. Teratogenicity and Reproductive Effects. There are no published animal studies available that adequately assess the teratogenic or adverse reproductive potential of CFC-113. Although there are industry-sponsored animal studies in progress, uncertainty about these biological endpoints in humans should serve as a stimulus for future research.
4. Mutagenicity. Because of the limited testing performed, further testing is needed before definitive conclusions can be drawn.

# 2. INTRODUCTION

The principal intent of this document is to evaluate health effects associated with exposure to chlorofluorocarbon - 113 (CFC-113). Chlorofluorocarbon 113 is released into environmental air as a result of evaporative loss during production, storage, consumer, and manufacturing uses. Since its atmospheric reactivity is sufficiently low to allow it to reach the stratosphere, CFC-113 is also of potential concern with regard to health effects of an indirect nature.

The nature of the known health effects primarily involve impairment of neurological and cognitive functions (humans) and the cardiovascular system (animals) following acute exposure to levels greatly exceeding 1,000 ppm (7,700 $mg/m^3$). The health information pertaining to CFC-113 is discussed in Chapter 5. In addition to evaluating the spectrum of health effects associated with CFC-113 release to the environment, this document also discusses analytical methods, production, sources, emissions, and ambient concentrations to place CFC-113 in a real-world perspective. These aspects are discussed at the outset, in Chapter 3.

In recent years, a great deal of attention has been focused upon the role of chlorofluorocarbons, including CFC-113, and related species in possible perturbations of stratospheric ozone ($O_3$). Biologically damaging ultraviolet radiation incident at the Earth's surface would be increased by actual $O_3$ depletion; and it is hypothesized that, as a result, an increase in the incidence of non-melanoma skin cancers might occur.

A comprehensive discussion of the role of chlorofluorocarbons in the photocatalytic destruction of stratospheric $O_3$ is beyond the scope of this document. This area of stratospheric chemistry is rapidly changing with regard to refinements of atmospheric models and reaction kinetics. For a more detailed discussion, the reader is referred to publications of The National Research Council (NRC) (1979a, b; 1982) and The World Meteorological Organization (WMO) (1982). The role of all chlorofluorcarbons in perturbations of stratospheric $O_3$ is an area of ongoing interest in the U.S. EPA Office of Toxic Substances. This health assessment document, however, does summarize the major findings of these groups in relation to estimates of stratospheric $O_3$ change associated with chlorofluorocarbons in general, and whenever possible, with



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CFC-113 in particular. It should be noted that CFC-113 is simply one member of a group of compounds that have the potential to alter stratospheric $O_3$ levels.

## 2.1 REFERENCES


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# 3. PHYSICO-CHEMICAL PROPERTIES, PRODUCTION AND ENVIRONMENTAL FATE

## 3.1 CHEMICAL AND PHYSICAL PROPERTIES

Chlorofluorocarbons, in general, are characterized by high density, low boiling point, low viscosity, low surface tension, and high thermal and photostability (Downing, 1966). They do not react with most metals below 200°C nor do they generally react with acids or oxidizing agents. However, specific and unusual applications should be carefully reviewed and tested. To a large degree, stability is attributed to the number of C-F bonds--bonds exhibiting high bond strength (Bower, 1971).

Trichlorotrifluoroethane, $CCl_2F\text{-}CClF_2$ (CFC-113), is a nonflammable, colorless liquid, characterized by a moderately high vapor pressure and a low boiling point (Table 3-1) and by high thermal and photolytic stability. It is practically insoluble in water, is heavier than water, and is extremely resistant to hydrolysis (E. I. duPont de Nemours, 1976). At equilibrium, with a partial pressure of one atmosphere and at 86°F, less than 0.005 grams of CFC-113 per liter of water per year is hydrolyzed (E. I. duPont de Nemours, 1980). Its solubility in water, per atmosphere of partial pressure at 25°C, is 0.017 grams per 100 grams of water (E. I. duPont de Nemours, 1980). While CFC-113, as others in this class, is relatively inert upon contact with common construction materials such as steel, copper, and aluminum, it has the potential to react violently with more reactive metals in their elemental state, e.g., sodium, potassium, and barium (E. I. duPont de Nemours, 1976). Zinc, magnesium, and aluminum alloys containing more than two percent magnesium are not recommended for use in systems where water may be present (Downing, 1966; E. I. duPont de Nemours, 1969). As a solvent, CFC-113 is often used in azeotropic mixtures with acetone, methylene chloride, and ethyl and methyl alcohol (Ward, 1981). Blends of CFC-113 and isopropyl alcohol are also used.

## 3.2 ANALYTICAL METHODOLOGY

Detecting extremely low levels of CFC-113 in ambient air requires sophisticated analytical techniques. The two most commonly used systems, both of which have a lower limit of detection on the order of a few parts per trillion (ppt), are gas chromatography-mass spectrometry (GC-MS) and gas chromatography-electron capture detection (GC-ECD). To measure workplace concentrations, GC coupled with flame ionization or thermal conductivity detectors is satisfactory.

TABLE 3-1. PHYSICAL PROPERTIES OF TRICHLOROTRIFLUOROETHANE*

| | |
|---|---|
| Molecular weight | 187.4 |
| Boiling point | 47.6°C (760 mm) |
| Vapor pressure | 6.5 lb/in$^2$ (25°C) |
| Density | 1.5 gm/cm$^3$ |
| Solubility | 0.017 gm/100 gm $H_2O$ (0°C, 760 mm) |

*Downing, 1966; E. I. duPont de Nemours, 1969, 1976.

3.2.1 Sampling

Because CFC-113 levels in air are typically in the sub parts-per-billion (ppb) range, the sampling and analysis techniques have been designed to detect trace levels. Singh et al. (1979a,b) have employed cryogenic trapping of air containing trace levels of CFC-113. During sampling, traps are maintained at liquid oxygen temperature. Traps were made of stainless steel packed with a 4-inch bed of glass wool or glass beads. Aliquots are thermally desorbed and injected directly into the gas chromatograph. More recently, Singh et al. (1981b) collected air samples in precleaned, 1-liter electropolished stainless-steel canisters. Samples were then preconcentrated at liquid oxygen temperature in freezeout traps containing SE-30 or glass wool.

Makide et al. (1980) used electropolished stainless-steel canisters, followed by preconcentration on a silicone OV-101 column at - 40°C. Column temperature was raised at a rate of 5°C per minute up to 70°C for separation of components.

3.2.2 Analysis

Cronn and Harsch (1979) reported a detection limit of 12 ppt (at a mixing ratio of 50 ppt) with GC-MS. Precision was 10 percent. A lower detection limit (2 ppt) had been obtained using GC-ECD (Harsch and Cronn, 1978). In this system, the CFC-113 mixing ratio was 23 ppt and precision was again 10 percent. Cronn and coworkers have reported difficulties in measuring low levels of CFC-113 in samples collected at high altitudes (Harsch and Cronn, 1978). Contamination resulted when the mixing ratio of CFC-113 in the laboratory air was in the range of 15 to 20 ppb (0.116 to 0.154 mg/m$^3$).

Measurements of CFC-113 in rural air samples by GC-ECD using a freezeout concentration technique resulted in a detection limit of 0.8 ppt with a precision of 1.8 percent at a mixing ratio of 21 ppt (Rasmussen et al., 1977).

In a comparison of GC-ECD with GC-MS, Cronn et al. (Cronn and Harsch, 1979; Cronn et al., 1976a) judged GC-ECD to be superior in reproducibility and in yielding a lower limit of detection. Since the presence of water and oxygen in the EC detector may cause erroneous results for some compounds, Russell and Shadoff (1977) recommended that oxygen be eliminated during preconcentration procedures, while water could be removed through the use of drying tubes.

The lowest detection limit reported is that of Makide et al. (1980), <0.05 ppt with a GC-ECD system.

Fabian et al. (1981), using cryogenic sampling with GC/MS analysis, reported a detection limit for CFC-113 of about 0.1 ppt for a 1-liter sample. It was indicated that CFC-113 is stable in stainless steel bottles electropolished internally, for more than 6 months.

3.2.3 Calibration

Gas chromatographs have generally been calibrated with static dilutions of ppm-level standards (Harsch and Cronn, 1978; Rasmussen et al., 1977; Makide et al., 1980) and by use of permeation tubes (Singh et al. 1981b).

Singh et al. (1977a) judged FEP Teflon® tubing to be satisfactory in generating primary standards for CFC-113. All tubing materials were either aluminum or glass. Errors in this approach were less than 10 percent. Similar results were recently reported by Singh et al. (1981b). Permeation rates were determined at 30 ± 0.05 °C. Error was < ± 10 percent. Cell permeation tubes were conditioned for two weeks or longer. These investigators concluded that permeation tubes offer the most accurate means of generating primary standards.

3.3 PRODUCTION, USE, EMISSIONS, AND AMBIENT MIXING RATIOS

3.3.1 Production

Chlorofluorocarbons typically are produced by displacing chlorine from chlorocarbons by fluorine using hydrogen fluoride (HF). The starting material for CFC-113 is normally tetrachloroethylene (Ward, 1981). Other chlorocarbons commonly used include carbon tetrachloride ($CCl_4$), and hexachloroethane ($C_2Cl_6$).

A reaction sequence employing $C_2Cl_4$ (tetrachloroethylene) to produce CFC-113 is depicted as follows:

$$C_2Cl_4 + 3\ HF \xrightarrow[Cl_2]{SbCl_5} C_2Cl_3F_3 + 3\ HCl$$

45-200°C

In this method, chlorine gas ($Cl_2$) maintains the antimony pentachloride ($SbCl_5$) catalyst in the pentavalent state (Ward, 1981). The reaction can proceed either in the liquid or vapor phase. Anhydrous hydrogen chloride (HCl) is the principal byproduct.

Only two manufacturers currently produce CFC-113 in the United States: Allied Chemical Corporation, Baton Rouge, Louisiana (SRI Inter., 1979) and E. I. duPont de Nemours and Company, Inc., at its Montague, Michigan and Corpus Christi, Texas plants (Ward, 1981).

Accurate U.S. production data for CFC-113 are not readily available. Production rates for 1979 are estimated to be about 59,000 metric tons (E. I. duPont de Nemours, 1982). The RAND Corporation (U.S. EPA, 1980a) estimated that production of CFC-113 in 1977 amounted to about 37,000 metric tons (upper bound) of which solvent application accounted for 96 percent of the CFC-113 available for use. The U.S. EPA (1980a) has estimated that by 1990, 71,000 metric tons could represent an upper bound estimate of production.

3.3.2 Use

Principal uses of CFC-113 fall into several main categories (NRC, 1979a): (1) degreasing, cleaning, and drying applications; (2) removal of solder flux; (3) critical cleaning of electronic, electrical and mechanical assemblies; (4) application as a cutting fluid, carrier and reaction medium, and dry cleaning solvent. It is an alternative to tetrachloroethylene, currently the solvent of choice in the drycleaning industry (Fischer, 1980). It is not used in aerosol formulations as a propellant or as a propellant component, but is used as a solvent or active ingredient in certain aerosol formulations.

In cleaning and drying operations, two types of solvent losses occur (U.S. EPA, 1980b): (1) escape in vapor form and (2) in liquid form when tanks are emptied for cleaning. Although there are no identified reports that CFC-113 has been detected in surface or drinking waters, this potential exists since CFC-113 may be sealed in drums and buried. Because CFC-113 has very limited solubility in water and is highly volatile, all releases of CFC-113 can be expected to eventually be conveyed to the stratosphere.

Estimates of the NRC (1979a) suggest that CFC-113 emissions during the period 1976-1977 were 30,000 metric tons. CFC-113 was reported to account for over 15 percent of chlorofluorocarbon emissions (U.S. EPA, 1980a). The World Meteorological Organization (1982), citing figures supplied by E. I. duPont de Nemours and Company, reported a current global annual emissions rate of 91,000 metric tons.

The NRC (1979a) estimated 1976-1977 emissions in the United States by use category as follows: (1) degreasing, cleaning, and drying, 5,909 metric tons; (2) solder flux removal, 6,818 metric tons; (3) critical cleaning and drying, 11,818 metric tons; and (4) miscellaneous, 5,454 metric tons (909 metric tons associated with dry cleaning applications). Substitution of alternative solvents was considered a possibility to somewhat reduce emissions of CFC-113 in all use categories except (3), where no alternative solvent is available.

In a RAND Corporation report (U.S. EPA, 1980a), all CFC-113 produced for nonaerosol end uses was expected to "find its way into the ambient air." CFC-113 accounts for less than one percent of the market for solvents to dryclean clothes (U.S. EPA, 1980a). In 1976, about 3 percent of CFC-113 sold in the United States was used as an inert carrier (U.S. EPA, 1980a). Assuming prompt emissions, the RAND estimate for emissions is 35,000 metric tons (U.S. EPA, 1980b).

### 3.3.3 Ambient Air Mixing Ratios

The extent to which emissions of CFC-113 contribute to the loading of the atmosphere is indicated by measurements of ambient air mixing ratios shown in Table 3-2.

The most recently reported mixing ratios for the northern and southern hemispheres are those of the World Meteorological Organization (1982). Based upon the observations of Singh et al. (1981b) and Rasmussen et al. (1981), the WMO reported ranges of 12 to 25 ppt (northern hemisphere) and 11 to 22 ppt (southern hemisphere). The estimated limit of detection was 1 ppt with the estimated accuracy at 20 percent and the estimated precision at 10 percent. Singh et al., (1981b) reported an average atmospheric growth rate for CFC-113 of 2 ppt per year, based on measurements made at Point Arena, California, a "clean" air site, from late 1979 to early 1981.

Measurements made in the latter part of 1977 indicated a global average mixing ratio of 18 ppt (Singh et al. 1979a, b); no gradient was observed between the northern and southern hemispheres. In comparison, the two most

TABLE 3-2. TROPOSPHERIC LEVELS OF CFC-113

| Location | Date of measurement | Concentration (ppb) max | min | average | Reference |
|---|---|---|---|---|---|
| Arizona | | | | | |
| Phoenix | 4/23/79 - 5/6/79 | 1.2513 | 0.0122 | 0.1513 ± 0.2247 | Singh et al., 1981a |
| California | | | | | |
| Badger Pass | 5/5/77 - 5/13/77 | 0.255 | 0.014 | 0.027 ± 0.026 | Singh et al., 1979b |
| Los Angeles | 4/9/79 - 4/21/79 | 4.160 | 0.049 | 0.305 ± 0.6671 | Singh et al., 1982 |
| | 4/28/76 - 5/4/76 | 0.398 | 0.029 | 0.119 ± 0.077 | Singh et al., 1977b |
| Point Reyes | 12/1/75 - 12/12/75 | 0.450 | 0.012 | 0.031 ± 0.041 | Singh et al., 1977b;1979b |
| Mill Valley | 1/11/77 - 1/12/77 | 0.181 | 0.017 | 0.042 ± 0.026 | Singh et al., 1979b |
| Oakland | 6/28/79 - 7/10/79 | 0.309 | 0.016 | 0.049 ± 0.059 | Singh et al., 1982 |
| Palm Springs | 5/5/76 - 5/11/76 | 0.105 | 0.012 | 0.037 ± 0.013 | Singh et al., 1979b |
| Point Arena | 5/23/77 - 5/30/77 | 0.042 | 0.014 | 0.023 ± 0.006 | Ibid |
| | 8/30/78 - 9/5/78 | 0.027 | 0.018 | 0.022 ± 0.002 | Ibid |
| | 12/8/79 - 2/18/81 | 0.137 | 0.024 | 0.025 | Singh et al., 1981b |
| Riverside | 4/25/77 - 5/4/77 | 0.144 | 0.020 | 0.099 ± 0.166 | Ibid |
| | 7/1/80 - 7/13/80 | 2.21 | 0.026 | 0.274 ± 0.262 | Singh et al., 1982 |
| San Jose | 8/21/78 - 8/27/78 | 0.365 | 0.017 | 0.076 ± 0.068 | Singh et al., 1979b |
| Stanford Hills | 11/23/75 - 11/30/75 | 0.157 | 0.008 | 0.031 ± 0.030 | Singh et al., 1977b;1979b |
| Yosemite | 5/12/76 - 5/18/76 | 0.031 | 0.011 | 0.020 ± 0.003 | Ibid |
| Colorado | | | | | |
| Denver | 6/15/80 - 6/28/80 | 1.608 | 0.028 | 0.221 ± 0.235 | Singh et al., 1982 |
| Delaware | | | | | |
| Delaware City | 7/8/74 - 7/10/74 | <0.01 | <0.01 | -- | Lillian et al., 1975 |
| Illinois | | | | | |
| Chicago | 4/20/81 - 5/2/81 | 0.359 | 0.020 | 0.082 ± 0.065 | Singh et al., 1982 |

TABLE 3-2. (continued)

| Location | Date of measurement | Concentration (ppb) max | min | average | Reference |
|---|---|---|---|---|---|
| Kansas | | | | | |
| Jetmore | 6/1/78 - 6/7/78 | 0.040 | 0.012 | 0.023 ± 0.005 | Singh et al., 1979b |
| Maryland | | | | | |
| Baltimore | 7/11/74 - 7/12/74 | 0.038 | <0.01 | 0.03 | Lillian et al., 1975 |
| Missouri | | | | | |
| St. Louis | 5/29/80 - 6/9/80 | 1.792 | 0.022 | 0.132 ± 0.171 | Singh, et al., 1982 |
| Nevada | | | | | |
| Reese River | 5/14/77 - 5/20/77 | 0.042 | 0.004 | 0.019 ± 0.006 | Singh et al., 1979b |
| New Jersey | | | | | |
| Bayonne | 3/73 - 12/73 | 38 | <0.01 | 4.12 | Lillian et al., 1975 |
| Sandy Hook | 7/2/74 - 7/5/74 | 0.56 | <0.01 | <0.08 | Ibid |
| Seagirt | 6/18/74 - 6/19/74 | <0.01 | <0.01 | <0.01 | Ibid |
| New York | | | | | |
| New York City | 6/27/74 - 6/28/74 | 0.025 | <0.01 | 0.025 | Ibid |
| Staten Island | 3/26/81 - 4/5/81 | 0.359 | 0.059 | 0.129 ± 0.078 | Singh, et al., 1982 |
| White Face Mtn. | 9/16/74 - 9/19/74 | <0.01 | <0.01 | -- | Lillian et al., 1975 |
| Ohio | | | | | |
| Wilmington | 7/16/74 - 7/26/74 | 0.075 | <0.01 | 0.016 | Ibid |
| Pennsylvania | | | | | |
| Pittsburgh | 4/7/81 - 4/17/81 | 0.162 | 0.042 | 0.068 ± 0.027 | Singh, et al., 1982 |
| Texas | | | | | |
| Houston | 5/14/80 - 5/25/80 | 1.664 | 0.037 | 0.199 ± 0.190 | Singh, et al., 1982 |
| Japan | | | | | |
| 9 rural sites | 8/78 - 9/78 | 0.027 | 0.021 | 0.023 ± 0.0016 | Makide et al., 1980 |

dominant chlorofluorocarbons (methane series), CFC-11 and CFC-12, were found at global average mixing ratios of 126 and 220 ppt, respectively. Singh et al. (1979a,b) expected the stratosphere to be the major reservoir for CFC-113. Despite extensive study, significant tropospheric sinks for CFC-11, CFC-12, and CFC-113 have not been confirmed or quantified (NRC, 1979a, b.)

Rasmussen and Khalil (1982) measured the global concentration distribution of CFC-113 in air samples collected by aircraft in 1978. They found that CFC-113 was equally distributed in and above the boundary layer (at altitudes of 0.12-0.36 km and 4.8-5.9 km, respectively), and equally distributed in latitude. The average ratio was reported to be 13 ppt.

In flights over the Pacific Northwest in March 1976, Cronn and coworkers (1976b) detected CFC-113 in the upper troposphere at an average mixing ratio of 21 ± 4 ppt ($0.17 \pm 0.03 \times 10^{-3}$ mg/m$^3$). More recently, Cronn et al. (1977a, b) have detected CFC-113 in whole-air samples collected during high altitude tropospheric flights over the Pacific Ocean west of San Francisco (37° N). An average northern hemisphere tropospheric background mixing ratio of 18 ± 2.3 ppt ($0.14 \pm 0.02 \times 10^{-3}$ mg/m$^3$) was measured (April 1977).

Fabian et al. (1981) are the first investigators to have measured CFC-113 levels in the stratosphere; samples were collected during balloon descent, from 28.8 to 14.4 kilometers. The vertical profile obtained suggests that CFC-113 is rapidly decomposed; at 15 kilometers, the CFC-113 mixing ratio was 10 ppt and had decreased to 0.6 ppt at 28.8 kilometers.

3.3.4 Other Media

No information is available regarding levels of CFC-113 in water or soil.

3.4 ATMOSPHERIC FATE

The potential for ambient air mixing ratios of CFC-113 to pose a hazard to human health is influenced by many processes, one of which involves transport of CFC-113 to the stratosphere where it participates in ozone ($O_3$) perturbation reactions.

It is generally accepted that the longer the tropospheric residence time for a chemical species, the greater the likelihood of diffusion into the stratosphere. Current understanding of stratospheric science suggests that many substances produced by human activities have the potential to alter stratospheric $O_3$ levels. A major goal of atmospheric scientists is to determine the net effect of all these substances on $O_3$ simultaneously.

Chlorofluorocarbons are remarkably stable in the troposphere. However, they do undergo photodissociation in the stratosphere (NRC 1979a, b; NRC 1982;

WMO, 1982). In a report prepared for the U. S. Environmental Protection Agency by the Rand Corporation (U.S. EPA 1980a), CFC-113 was described as highly unreactive and unlikely to decompose prior to entering the stratosphere.

There are no known tropospheric sinks for CFC-113. Hester et al. (1974) reported that no detectable loss of CFC-113 occurs when it is irradiated, under simulated atmospheric conditions, in the presence of olefins and nitrogen oxides. The possibility exists that some decomposition of chlorofluorocarbons may occur upon contact with hot desert sands (NRC, 1979a).

There are two processes for CFC-113 destruction: direct photolysis and reaction with excited atomic oxygen, the latter being produced upon photodissociation of $O_3$. Calculations made by Chou et al. (1978) indicate that photodissociation in the stratosphere accounts for 84 to 89 percent of CFC-113 removal. An atmospheric lifetime, based upon measured absorption coefficients, in the range of 63 to 122 years was estimated. An atmospheric lifetime of 88 years was estimated by Wuebbles (1983) using the one-dimensional (1-D) transport-kinetics model of The Lawrence Livermore National Laboratory.

The wavelength region associated with the photodissociation of chlorofluorocarbons is the range from 185 to 227 nm between the Schumann-Runge absorption band for $O_2$ and the Hartley band for $O_3$. Atkinson et al. (1976) concluded that chlorofluorocarbons with two or more chlorine atoms had sufficiently high ultraviolet absorption in this range that photodissociation was the predominant mode of decomposition in the critical region (30 kilometers) of the stratosphere.

The absorption cross section for CFC-113 over the 185 to 227 nm wavelength range indicates that CFC-113 has approximately the same potential for photodissociation as dichlorodifluoromethane (CFC-12), but less than that for trichlorofluoromethane (CFC-11) (Chou et al., 1978). Upon complete photodissociation, each molecule of CFC-113 and CFC-11 yields an equal number of Cl atoms. The absorption maxima of CFC-113 and CFC-12 in the near ultraviolet are 160 nm and 177 nm, respectively (Sandorfy, 1976); the absorption maximum of CFC-11 is at a higher wavelength, 185 nm. In this narrow wavelength range, absorption of UV by $O_3$ is at a minimum, thus allowing for absorption (consequently, destruction) by chlorofluorocarbons.

As shown in the following reaction sequence, release of atomic chlorine (Cl) leads to the photocatalytic conversion of $O_3$ and O to oxygen:

$$CCl_2F - CClF_2 \xrightarrow{h\nu} CClF - CClF_2 + Cl\cdot$$

$$Cl\cdot + O_3 \longrightarrow ClO + O_2$$

$$ClO + O \longrightarrow Cl\cdot + O_2$$

Atomic chlorine, produced in the first reaction, would react with $O_3$ to yield chlorine oxide (ClO) that, upon subsequent reaction would form a chain reaction in theory.

As noted by the World Meteorological Organization (1982), the efficiency of this cycling is closely coupled with other cycles, principally the nitrogen oxides and hydroxyl radical cycles. In addition, efficiency is, in part, determined by perturbations in atmospheric temperature such as the stratospheric cooling resulting from increases in carbon dioxide levels in the troposphere (WMO; NRC, 1982; Wuebbles, 1983).

The National Research Council (1982), drawing upon the data base developed by the World Meteorological Organization (1982), recognized CFC-113 to have the potential to perturb stratospheric $O_3$ levels. The Council has stated that "The abundance of ozone in the stratosphere is determined by a dynamic balance among processes that produce and destroy it and transport it to the troposphere." Thus, the actual role of CFC-113 in stratospheric processes can best be elucidated through an examination of multiple perturbation scenarios involving all the known key contributory factors (NRC, 1982). The potential of CFC-113, however, can be examined in a context apart from other perturbation processes. In this manner, important information concerning the atmospheric chemistry of CFC-113 can be used to develop more representative multiple perturbation simulations. The development of such models has been recommended by the Council to describe the combined effects of all relevant compounds on stratospheric $O_3$.

Wuebbles (1983) has recently provided a theoretical framework in order to assess the potential impact of all chlorocarbons presently thought to be of concern regarding $O_3$. Ameloriating effects of other anthropogenic substances were not included. Assessments were based upon model calculations using the one-dimensional coupled transport and chemical kinetics model of the troposphere and stratosphere developed at the Lawrence Livermore National Laboratory. Although the chemistry presently used in the model represents the best current

evaluation of existing laboratory data, Wuebbles noted that changes in the chemistry are likely to continue. Wuebbles concluded that, if chlorocarbons alone are considered, CFC-113 and other chlorocarbons could contribute significantly to predicted changes in total $O_3$ based upon their current emission rates.

Wuebbles et al. (1983) extended his "chlorocarbon-only" analyses by examining the coupling between several possible anthropogenic sources ($CO_2$, $N_2O$, and $NO_x$) of stratospheric perturbations of past and future changes in total $O_3$. Surface methane ($CH_4$) was held constant. They found, using the Lawrence Livermore one-dimensional transport-kinetics model, that "$CO_2$ and $NO_x$ emissions have comparable ameliorating effects on the total ozone decrease otherwise expected from chlorofluorocarbon emissions.... When all anthropogenic sources are included the change in total ozone is less than 1% over the next 120 years." Calculations indicated that when all anthropogenic sources were considered, the change in total $O_3$ over the 1970-1980 timeframe was +0.13 percent, consistent with available statistical $O_3$ trend analyses.

The recent model calculations of Owens et al. (1982) suggest that natural and anthropogenic emissions of methane also may significantly moderate the $O_3$ destroying potential of chlorofluorocarbons. Using a 1-D model with chemical reaction rates and incident solar fluxes recommended by WMO (1982), Owens and coworkers have calculated that a doubling of methane, if viewed in isolation, can lead to a total column $O_3$ increase of 3.5 percent. When coupled with chlorofluorocarbons, the calculation shows an overall total column $O_3$ change of -1.6 percent. Khalil and Rasmussen (1982) also recently suggested that an increase in the atmospheric levels of methane may serve to protect $O_3$ levels in the stratosphere. After examining measurement data as far back as 1965, they find the data consistent with a rate of increase in methane ranging from 1.2 to 2 percent per year. State-of-the-art instrumentation and statistical methodology indicate that detection of global average stratospheric $O_3$ trends is limited to about a 2 percent change per decade. At the present time, the direction and extent of $O_3$ perturbation cannot be measured. Wuebbles et al. (1983) reported that a doubling of the present surface $CH_4$ concentration, in the Lawrence Livermore model, would increase total $O_3$ by 2 percent. Because of difficulties in predicting future trends in atmospheric $CH_4$, Wuebbles et al. held surface $CH_4$ constant in their calculations.

Among the confounding factors are the uncertainties and limitations of the models and the complexity of rapidly changing knowledge in atmospheric chemistry. The NRC (1982) stated that "These results should be interpreted in light of the uncertainties and insufficiencies of the models and observations." An evaluation of the impact of CFC-113 upon stratospheric and thus on total column $O_3$ must take into account all factors affecting stratospheric and tropospheric processes if realistic estimates of $O_3$ perturbations are to be made.

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# 4. METABOLIC FATE AND DISPOSITION

## 4.1 ABSORPTION AND ELIMINATION

Use of CFC-113 as a solvent for degreasing fabricated metal parts and dry cleaning of fabrics suggests that workers will primarily be exposed through inhalation and contact with the skin.

Limited information has been published concerning the fate and disposition of CFC-113 and related compounds. Most of the data were necessarily obtained through experimentation on rodent species and at inhalation exposure levels well above ambient tropospheric levels.

Chlorofluorocarbons were judged to be absorbed by dogs through inhalation in the following descending order: CFC-11 > CFC-113 > CFC-12 > CFC-114 (Shargel and Koss, 1972). Levels were determined in arterial and venous blood of anesthetized male and female dogs following exposure to an aerosol mixture containing 25 percent (by weight) of each compound. Blood samples were extracted with hexane prior to quantitation by gas chromatography-electron capture detection. Peak arterial levels accounted for only a small percentage of total administered dose.

In general, fluorocarbons and chlorofluorocarbons exhibit biphasic absorption patterns (Azar et al., 1973; Letkiewicz, 1976; Trochimowicz et al., 1974). A rapid initial increase in blood levels is followed by a slower increase to maximum concentrations. Equilibrium is reached when arterial and venous blood concentrations are equal. During elimination, there is a rapid initial fall in blood levels followed by a slower decline to undetectable levels. During elimination, venous concentrations exceed arterial concentrations, indicating that fluorocarbons are being released from tissues.

Dermal absorption of CFC-113 has been evaluated in man (Haskell Laboratory, 1968). Three subjects were tested. Concentration of CFC-113 in alveolar air was used as an indication of CFC-113 absorption. The subjects had their hands and forearms exposed for thirty minutes, and portions of their scalps exposed for fifteen minutes. The concentration of CFC-113 in their breath was then measured at various times after termination of the exposure.

The data are presented in Table 4-1. At 90 minutes post-exposure, the concentrations of CFC-113 in exhaled air in all three subjects had decreased from a high of 12 ppm (92 $mg/m^3$) to less than 0.5 ppm (3.8 $mg/m^3$). In one of the subjects, a trace concentration of 0.1 ppm (0.7 $mg/m^3$), the limit of



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TABLE 4-1. DERMAL EXPOSURE OF MAN TO CFC-113

| Area exposed | Duration of exposure | Time of peak* in expired breath | Value of peak |
|---|---|---|---|
| Portions of scalp | 15 min. | 20.5 min. | 12.7 ppm |
| Portions of scalp | 15 min. | 18.5 min. | 7.4 ppm |
| Hands and forearms | 30 min. | 11.5 min. | 9.6 ppm |
| Hands and forearms | 30 min. | 23 min. | 1.7 ppm |

*Expressed in minutes after termination of exposure; at 90 minutes post-exposure, exhaled concentration was 0.5 ppm for all four exposures.

Data from Haskell Laboratory, 1968.

detectability in this test, remained 18 hours post-exposure. These data indicate that the human body absorbs CFC-113 as a result of dermal exposure, and that the amount of CFC-113 absorbed rapidly declines when the exposure ends.

Administration of CFC-12 and CFC-114 to dogs by various routes of exposure indicate that chlorofluorocarbons are eliminated solely via the respiratory tract (Matsumato et al., 1968).

4.2 DISTRIBUTION AND METABOLISM

Chlorofluorocarbon 113 can be expected to partition into lipid-rich tissues during continuous exposure, until equilibrium or steady-state conditions are reached. During the rapid rise to maximal blood concentration, arterial concentrations of chlorofluorocarbons have been observed to be greater than venous concentrations (Azar et al., 1973). Blood levels of CFC-113 and other fluorocarbons were measured in beagle dogs during experiments reported by Trochimowicz et al. (1974). Animals were exposed for 10 minutes to 0.1 percent (1,000 ppm; 7,700 $mg/m^3$), 0.5 percent (5,000 ppm; 38,500 $mg/m^3$), and 1.0 percent (10,000 ppm; 77,000 $mg/m^3$) CFC-113. The investigators recorded higher levels in arterial blood during exposure and lower levels post exposure. The authors suggested that these observations reflect an uptake and release by body tissues. At exposure levels (5,000 ppm; 38,500 $mg/m^3$) which have sensitized the heart to exogenous epinephrine, arterial blood levels of 12.5 µg/ml and venous blood levels of 4.9 µg/ml were observed (at 5 minutes of exposure). CFC-113 was extracted from blood with hexane and analyzed by GC-ECD.

Carter et al. (1970) detected CFC-113 in brain, liver, heart, and fat of rats exposed, via inhalation, for 7 to 14 days. Levels are shown in Table 4-2. Similar findings have recently been reported by Savolainen and Pfäffli (1980). Male Wistar rats exposed to 200, 1,000, and 2,000 ppm (1,540, 7,700, 15,400 $mg/m^3$) of CFC-113 vapor for 2 weeks, 5 days per week, 6 hours daily exhibited a dose-dependent partitioning of the compound into perirenal fat and to a much lesser extent into brain. An approximate 7 to 9 hour half-time of diminution from adipose tissue is suggested by post-exposure tissue analysis. The neurochemical effects of CFC-113 exposure were examined by measuring levels of RNA, glutathione, and oxidative enzymes in brain tissue. After the second week of exposure to 1,000 ppm (7,700 $mg/m^3$), cerebral RNA levels were 14.1 ± 0.7 nmoles/mg protein. Corresponding controls were 12.8 ± 1.0 nmoles/mg protein. This was statistically significant at $p < 0.05$. Glutathione levels, after one week of exposure of animals to 2,000 ppm, were lower than controls at $p < 0.01$ (2.4 ± 0.05 nmoles/mg protein compared to 2.6 ± 0.07 nmoles/mg protein. Glutathione peroxidase, an enzyme which protects cells from oxidative damage, was decreased ($p < 0.01$), compared to controls, following the second week of exposure to 2,000 ppm (15,400 $mg/m^3$). Exposed animals had a level of 17.5 ± 1.0 nmoles/mg protein compared to 20.6 ± 0.5 for controls. When rats were withdrawn from exposure to 2,000 ppm for 7 days, cerebral RNA

TABLE 4-2. MEAN TISSUE CONCENTRATIONS OF CFC-113 FROM RATS EXPOSED TO 2,000 PPM (Carter et al., 1970)

| | Exposure | | Postexposure | |
|---|---|---|---|---|
| Tissue | 7 days | 14 days | 24 hours | 48 hours |
| Brain (µg/gm) | 22.73 ± 1.00 | 22.65 ± 1.33 | none | none |
| Liver (µg/gm) | 15.77 ± 0.87 | 16.40 ± 1.72 | none | none |
| Heart (µg/gm) | 16.59 ± 2.56 | 15.03 ± 2.51 | none | none |
| Fat (µg/gm) | 722.48 ± 71.29 | 659.24 ± 21.17 | 108.45 ± 33.62 | 5.60 ± 2.94 |
| Adrenal (µg) | 8.39 ± 2.61 | 3.47 ± 0.34 | none | none |
| Thyroid (µg) | 1.09 ± 0.46 | 0.94 ± 2.00 | none | none |

decreased from a level of 13.1 ± 0.4 nmoles/mg protein (controls) to 12.6 ± 0.2 ($p < 0.05$). Differences in levels for glutathione and glutathione peroxidase during this period were no longer observed.

Vainio et al. (1980) observed *in vivo* effects of CFC-113 on a number of hepatic drug metabolizing enzymes. Male Wistar rats were exposed to 200, 1,000 or 2,000 ppm (1,540, 7,700, or 15,400 mg/m$^3$) CFC-113, 5 days per week, 6 hours daily for 1 or 2 weeks. Animals were sacrificed immediately after exposure. NADPH cytochrome c reductase activity decreased 36 percent ($p<0.01$) and 19 percent ($p<0.05$) after 1 and 2 weeks of exposure, respectively, to 2,000 ppm. The apparent recovery of reductase activity during the second week is unexplained. Microsomal cytochrome P-450 showed a statistically significant decline after 1 week of exposure to 1,000 ppm (7,700 mg/m$^3$) ($p<0.01$) and 2,000 ppm (15,400 mg/m$^3$) ($p<0.01$). UDP glucuronosyltransferase showed a dose-related increase in activity after 2 weeks of exposure of rats to 1,000 ppm (7,700 mg/m$^3$) ($p<0.01$) and after 1 and 2 weeks of exposure to 2,000 ppm (15,400 mg/m$^3$) ($p<0.01$ and $<0.05$, respectively). UDP glucuronosyltransferase is a detoxification enzyme dependent on membrane integrity. Whether the preceding changes represent an adverse effect for instance, a potential perturbance of microsomal membrane integrity, or merely an accomodative effect, is unknown. Glutathione content showed a statistically significant decrease ($p<0.05$) after only 2 weeks of exposure at the 2,000 ppm (15,400 mg/m$^3$) level.

Evidence also was presented indicating that CFC-113 was bound to cytochrome P-450 in the hepatic microsomes from uninduced and phenobarbital-induced rats. Phenobarbital treatment increased the affinity of CFC-113 to cytochrome P-450, as judged from the decrease in the apparent spectral dissociation constant obtained from a type 1 difference spectrum. The observed binding does suggest that CFC-113 may be a substrate for the mixed function oxidases.

These enzymatic changes accompanied cellular changes in hepatocytes and are described in section 5.1.4.

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# 5. HEALTH EFFECTS

The impact of CFC-113 upon human health must be viewed from two perspectives: (1) potential effects resulting from direct exposure to CFC-113 and (2) possible indirect effects resulting from CFC-113 perturbations of stratospheric $O_3$.

As discussed in earlier chapters, CFC-113 is transported to the stratosphere where it is calculated to photocatalytically destroy $O_3$ (Panofsky, 1978; Molina and Rowland, 1974). If sufficient depletion of stratospheric $O_3$ were to occur without an offsetting increase in tropospheric levels of $O_3$, more damaging ultraviolet (UV-B) radiation would reach the earth's surface. It is hypothesized that such increased UV-B radiation could result in an increase in the incidence of non-malignant skin cancers (NRC, 1982). The NRC (1982) estimated that there could be a 2 to 5 percent increase in basal cell (non-malignant) skin cancer incidence per 1 percent decrease in stratospheric $O_3$; and the increase in squamous cell skin cancer incidence could be about double that. The NRC (1982) concluded that the association between sunlight and melanoma is not strong enough to make a prediction of increased incidences due to increased exposure to UV based on epidemiological data. There are no empirical data which demonstrate such indirect effects (i.e. increased skin cancer incidence) to be associated with CFC-113 emissions; nor are such effects now thought to be likely in view of effects of various other air pollutants (e.g. CO, $NO_x$) on stratospheric ozone that have been calculated to offset any $O_3$ pertubations due to CFC-113 or other halocarbons (see Section 3.4 above). The ensuing discussion of CFC-113 health effects, therefore, focuses on the evaluation of animal and human studies of the direct effects of CFC-113.

## 5.1 ANIMAL STUDIES

### 5.1.1 Acute Toxicity

Acute inhalation exposures of various animal species to fluorocarbons at levels exceeding 25,000 ppm (192,500 $mg/m^3$) in inhaled air results in adverse effects. Exposures to concentrations between 50,000 and 250,000 ppm (385,000 and $1.925 \times 10^6$ $mg/m^3$) have been fatal. A characteristic feature of CFC-113 exposure is tachycardia and hypertension at 25,000 and 50,000 ppm (192,500 and 385,000 $mg/m^3$). High concentrations have induced cardiac arrhythmia in dog, sensitized the heart to the action of epinephrine in dog and mouse, and caused depression of myocardial contractility in dog.

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5.1.2 Cardiovascular and Respiratory Effects

5.1.2.1 Mouse--Aviado and Belej (1974) evaluated the ability of CFC-113 to induce cardiac arrhythmias and to sensitize the heart to epinephrine. In this study, male Swiss mice (25 to 35 grams) were anesthetized with sodium pentobarbital (i.v., 0.7 mg/10 g). A lead II electrocardiogram was used to monitor the cardiovascular response. There were three mice in each of four experimental groups. Group (1) inhaled 5 percent (50,000 ppm; 385,000 $mg/m^3$) CFC-113; group (2) inhaled 5 percent (50,000 ppm; 385,000 $mg/m^3$) CFC-113 plus a challenging dose of epinephrine 2 minutes after the initiation of inhalation; group (3) inhaled 10 percent (100,000 ppm; 770,000 $mg/m^3$) CFC-113; group (4) inhaled 10 percent (100,000 ppm; 770,000 $mg/m^3$) CFC-113 and a similar challenge schedule as described for (2). This dose of epinephrine (i.v., 60 µg/kg) was previously found to produce a transient and moderate cardiac acceleration.

The results of this study are presented in Table 5-1. CFC-113 at 5 percent (50,000 ppm; 385,000 $mg/m^3$) produced a response (ventricular ectopic beats) in the presence of a challenging dose of epinephrine while inhalation of 10 percent (100,000 ppm; 770,000 $mg/m^3$) CFC-113 resulted in cardiac abnormalities both with and without epinephrine.

5.1.2.2 Dog

5.1.2.2.1 In vitro. Aviado and Belej (1975) tested the ability of CFC-113 to depress myocardial contractility in a canine heart-lung preparation. The dogs were anesthetized with sodium pentobarbital (i.v., 30 mg/kg). The force of myocardial contractility was measured by a Walton strain-gauge and was plotted as ventricular function curves. The experimental groups consisted of three dogs each: group 1 inhaled 2.5 percent (25,000 ppm; 192,500 $mg/m^3$) CFC-113 and group 2 inhaled 5.0 percent (50,000 ppm; 385,000 $mg/m^3$) CFC-113.

The results are presented in Table 5-2 and Figure 5-1. Both 2.5 percent (25,000 ppm; 192,500 $mg/m^3$) and 5.0 percent (50,000; 385,000 $mg/m^3$) CFC-113 caused no decrease in myocardial contractility as measured by the strain-gauge while both ventricular function curves show a shift to the right. This shift indicates a decrease in ventricular output for the same filling pressure, or a decrease in myocardial contraction, indicating that the ventricular function curve is the more sensitive of the two measures. Both 2.5 percent (25,000 ppm; 192,500 $mg/m^3$) and 5.0 percent (50,000 ppm; 385,000 $mg/m^3$) CFC-113 caused myocardial depression in the canine heart-lung preparation.

TABLE 5-1. EFFECTS OF CFC-113 ON THE ELECTROCARDIOGRAM OF ANESTHETIZED MICE

| Concentration % V/V | Exposure to CFC-113 alone | | Exposure to CFC-113 and Epinephrine | |
|---|---|---|---|---|
| | No. of Exposures | Type of Arrhythmia (incidence) | No. of Exposures | Type of Arrhythmia (incidence) |
| 5 | 3 | none | 3 | ventricular ectopics (1) |
| 10 | 3 | inverted T wave (1) | 3 | ventricular bigeminy (3) |

Data from Aviado and Belej (1974).



TABLE 5-2. EFFECT OF CFC-113 ON THE CANINE HEART-LUNG PREPARATION: ADMINISTRATION OF 2.5 AND 5% PROPELLANTS TO HEART-LUNG PREPARATIONS FIXED AT 5 cm LEVEL OF VENOUS RESERVOIR (MEAN ± S.E.M.)

| Propellant fluorocarbon No. | Inhaled concentration | Number of preparations | Heart rate (beats/min) | | | Myocardial force (g) | | | Left atrial pressure (mm Hg) | | | Cardiac output (l/min) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control | Response | % Δ | Control | Response | % Δ | Control | Response | % Δ | Control | Response | % Δ |
| Trichlorotrifluoroethane CFC-113 | 2.5 | 3 | 147 ± 12.5 | 148 ± 10.6 | - 2 ± 1 | 82 ± 1.5 | 80 ± 0.6 | - 3 ± 1 | 2.9 ± 0.2 | 3.0 ± 0.2 | + 2 ± 3 | 1.31 ± 0.17 | 1.28 ± 0.02 | - 3 ± 1 |
| | 5.0 | 3 | 148 ± 13.1 | 150 ± 12.5 | - 1 ± 1 | 90 ± 2.7 | 86 ± 2.1 | - 4 ± 1 | 2.9 ± 0.2 | 3.0 ± 0.1 | + 3 ± 3 | 1.27 ± 0.02 | 1.23 ± 0.02 | - 3 ± 0.1 |

Data from Aviado and Belej (1975).

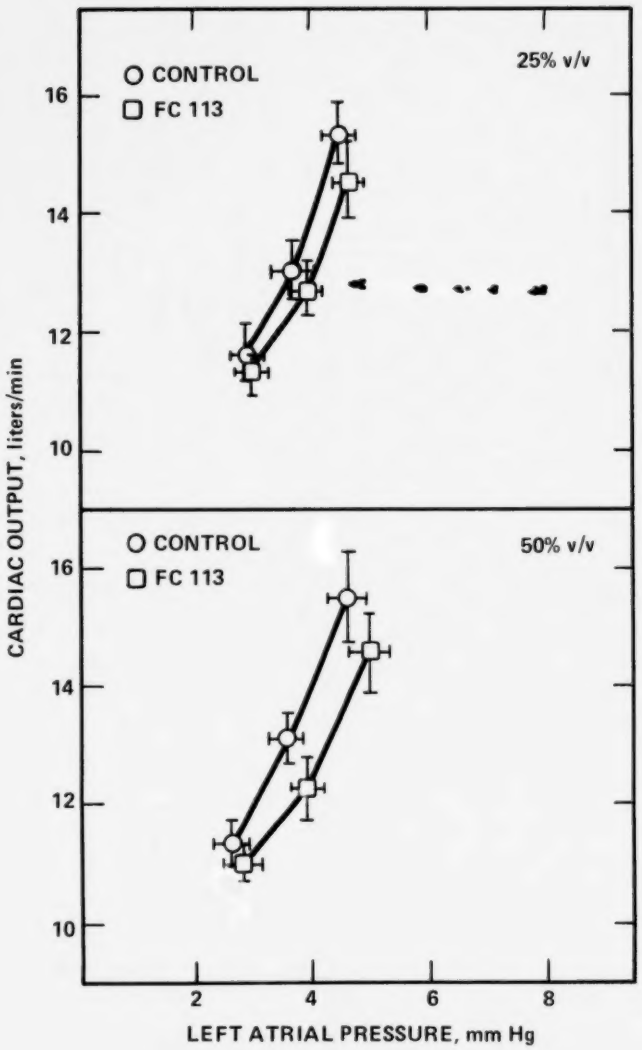


Figure 5-1. Ventricular function curves in canine heart-lung preparations before and during inhalation of 2.5 or 5.0% propellant in air. Each point represents the mean and standard error of the mean in groups of 3 preparations.

Source: Aviado and Belej (1975).

5.1.2.2.2 In vivo. Reinhardt et al. (1973) tested the ability of CFC-113 to sensitize the heart to exogenous epinephrine. Unanesthetized male beagle dogs were exposed to CFC-113 concentrations of 0.25 percent (2,500 ppm; 19,250 $mg/m^3$), 0.50 percent (5,000 ppm; 38,500 $mg/m^3$) and 1.0 percent (10,000 ppm; 77,000 $mg/m^3$). Electrocardiograph recordings monitored the cardiovascular response. A marked response (see Table 5-3) was defined as the development of a life-threatening arrhythmia (e.g., multiple consecutive ventricular beats) not present following the first (control) dose of epinephrine. Epinephrine was administered 5 minutes before and 5 minutes after the initiation of the 10 minute CFC-113 inhalation period following a 7-minute period of inhalation of room air. It was previously shown that doses of epinephrine (i.v., 8 µg/kg) administered 10 minutes apart did not produce additive effects. The results are presented in Table 5-3. No marked responses were observed in twelve exposures at 0.25 percent (2,500 ppm; 19,250 $mg/m^3$) CFC-113. CFC-113 causes cardiac sensitization to exogenous epinephrine at a CFC-113 concentration of 0.5 percent (5,000 ppm; 38,500 $mg/m^3$).

In an earlier unpublished report, Reinhardt and coworkers cautioned that results obtained at exogenous epinephrine concentrations should not be extrapolated to humans at lower chlorofluorocarbon exposure levels (Mullin et al., 1971). It was noted that a much higher concentration of chlorofluorocarbon (20,000 ppm; 154,000 $mg/m^3$) did not sensitize a dog's heart to the action of its own circulating level of epinephrine, even when this level was elevated through exercise. It was suggested that there is a considerable margin of safety between effect levels in dogs given exogenous epinephrine and levels that humans would normally experience. The rate of epinephrine secretion from the human adrenal gland in time of stress was reported to reach a level of 0.004 mg/kg/min (as cited in Mullin et al., 1971). Exogenous epinephrine, as employed in the Haskell Laboratory experiments, was reported to yield a dose of about 0.050 mg/kg/min, or ten times higher than a human would be likely to secrete in time of stress.

Clark and Tinston (1973) determined the $EC_{50}$ for the cardiac sensitizing effects of CFC-113 using unanesthetized beagle dogs (10-13 kg). Lead II electrocardiograms were recorded to monitor the cardiovascular response. The experimental groups consisted of four to seven dogs each. The dogs inhaled CFC-113 for 5 minutes, receiving equal doses of epinephrine (i.v., 5 µg/kg) 30 seconds before the end of the inhalation period and 10 minutes post-exposure.

Cardiac arrhythmias were never observed prior to the first or second injection of epinephrine even when it followed a challenge injection that had

TABLE 5-3. EFFECT OF CFC-113 ON CARDIAC SENSITIZATION TO EPINEPHRINE IN THE UNANESTHETIZED DOG

| Concentration of CFC-113 % (U/V) | | No. of Dog Exposures | No. of Marked Responses | % Marked Responses |
|---|---|---|---|---|
| Nominal | Analytical (gas. chrom.) | | | |
| 0.25 | 0.25 - 0.27 | 12 | 0 | 0.0 |
| 0.50 | 0.40 - 0.57 | 29 | 10 (1) | 34.5 |
| 1.0 | 0.90 - 0.95 | 4 | 3 (1) | 75.0 |

Numbers in parentheses indicate number of cases of ventricular fibrillation and cardiac arrest included in marked responses.

Data from Reinhardt et al. (1973).

caused an arrhythmia. At 1.0 percent (10,000 ppm; 77,000 mg/m$^3$) CFC-113, 50 percent of the animals can be sensitized to the effects of exogenous epinephrine with a 95 percent confidence interval of 0.5 percent to 1.4 percent around this value.

It should be pointed out that the above-mentioned cardiac sensitization studies are used to rank substances and because exogenous epinephrine was administered, cannot be extrapolated to human situations in which epinephrine is endogenously released in certain situations.

Blood levels of CFC-113 and other fluorocarbons in beagle dogs that are associated with the cardiac sensitizing effect of CFC-113 have been examined by Trochimowicz et al. (1974). Exogenous epinephrine was not administered to the animals. After recovery from surgery during which indwelling catheters were implanted, four dogs were exposed via face mask for 10 minutes to CFC-113 at levels of 0.1 percent (1,000 ppm; 7,700 mg/m$^3$), 0.5 percent (5,000 ppm; 38,500 mg/m$^3$), and 1.0 percent (10,000 ppm; 77,000 mg/m$^3$). The investigators recorded an arterial-venous difference during and after exposure. The authors suggested that this observation reflects an uptake by body tissues. After exposure, levels for all fluorocarbons were higher in venous blood. At the sensitizing level (5,000 ppm; 38,500 mg/m$^3$), blood concentrations of 12.5 µg/ml arterial blood and 4.9 µg/ml venous blood were recorded (at 5 minutes of exposure). At the TLV® (1,000 ppm; 7,700 mg/m$^3$), blood concentrations were 2.6 µg/ml (arterial) and 1.5 µg/ml (venous).

In a followup study, Trochimowicz et al. (1976) tested dogs with experimentally-induced myocardial infarctions to determine if heart damage might lower the apparent threshold for cardiac sensitization due to chlorofluorocarbons. Although CFC-113 was not used (methyl chloroform, trichlorofluoromethane, and bromotrifluoromethane were the test substances), the test results were reported to indicate that the halocarbons had no greater potential for cardiac sensitization among dogs having recovered from myocardial infarction than normal, healthy dogs. Concentrations of the test chemicals ranged from 0.25 percent (v/v) for methyl chloroform to 10 percent (v/v) for bromotrifluoromethane. The test method involved exposure to test chemicals, followed by an intravenous dose (8 µg/kg) of epinephrine, a dose which, given to animals exposed to air only, caused only mild ECG alterations.

Unpublished data of Mullin and coworkers (1971) suggest that, in beagle dogs trained to run on a treadmill (up to 16 minutes) while being exposed to CFC-113 (8 dogs to 10,000 ppm; 77,000 mg/m$^3$ and 4 dogs to 20,000 ppm; 154,000

$mg/m^3$), endogenous epinephrine is not high enough to cause cardiac arrhythmias at CFC-113 levels below 20,000 ppm (154,000 $mg/m^3$).

In cardiac sensitization studies conducted by E. I. duPont de Nemours and Company, it was concluded that CFC-113 is capable of sensitizing a dog's heart to exogenous epinephrine following exposure to concentrations between 2,000 to 2,500 ppm (15,400 to 19,250 $mg/m^3$) for periods of 0.5, 1, or 6 hours. One of six dogs exposed to 2,500 ppm (19,250 $mg/m^3$) for both 0.5 and 1 hour gave a marked response. However, it was reported that exposures (12) of dogs to concentrations of 10,000 ppm (77,000 $mg/m^3$) CFC-113 for a duration of 5 minutes did not cause cardiac arrhythmias in dogs frightened by a loud noise or electric shock (Haskell Laboratory, 1979).

5.1.2.3 Monkey--Belej et al. (1974) tested the effects of CFC-113 upon heart rate, myocardial force, aortic blood pressure, left atrial pressure, and pulmonary arterial pressure in anesthetized rhesus monkeys. The monkeys were anesthetized with sodium pentobarbital (i.v., 30 mg/kg), and their tracheas were cannulated for artificial respiration. A lead II EKG recorded cardiovascular responses; myocardial contraction was measured with a strain-gauge. The experimental groups, which consisted of three animals each, inhaled either 2.5 percent (25,000 ppm; 2,500 $mg/m^3$) or 5.0 percent (50,000 ppm; 385,000 $mg/m^3$) CFC-113 for 5 minutes alternating with inhalation of room air for 10 minutes.

The results presented in Table 5-4 indicate that 2.5 percent (25,000 ppm; 192,500 $mg/m^3$) CFC-113 is capable of inducing both tachycardia and myocardial depression. The authors report that both concentrations caused cardiac arrhythmias.

Aviado and Smith (1975) tested the effects of CFC-113 upon respiration and circulation using rhesus monkeys anesthetized with sodium pentobarbital (i.v., 30 mg/kg). The tracheas were cannulated for artificial respiration. Lead II EKG and femoral arterial blood pressure were continuously recorded. The following parameters were determined: pulmonary resistance, pulmonary compliance, and respiratory minute volume. Each test group consisted of three monkeys. Each group inhaled either 2.5 percent (25,000 ppm; 192,500 $mg/m^3$) or 5.0 percent (50,000 ppm; 385,000 $mg/m^3$) CFC-113 for 5 minutes, alternating with room air for 15 minutes.

The results are presented in Table 5-5: 2.5 percent (25,000 ppm; 192,500 $mg/m^3$) and 5.0 percent (50,000 ppm; 385,000 $mg/m^3$) CFC-113 caused a decrease in pulmonary resistance, an increase in pulmonary compliance, no change in

TABLE 5-4. RESPIRATORY AND CIRCULATORY EFFECTS OF CFC-113 UPON ANESTHETIZED RHESUS MONKEYS (BASED ON STUDY OF BELEJ AND COLLEAGUES)

| CFC-113 % Inhaled Concentration | Monkey # | Heart rate (beats/min) Control | Response | Δ % | Myocardial force (g) Control | Response | Δ % |
|---|---|---|---|---|---|---|---|
| 2.5 | 3 | 150.0<br>0.0 | 163.0<br>± 8.8 | + 8.9<br>± 5.9 | 47.5<br>± 7.7 | 38.4<br>± 4.2 | -17.1<br>± 6.8 |
| 5.0 | 3 | 155.0<br>± 2.9 | 185.0[a]<br>±13.2 | 19.8<br>±10.8 | 45.3<br>± 5.1 | 29.3<br>± 7.5 | -35.8<br>±12.6 |

| CFC-113 % Inhaled Concentration | Monkey # | Aortic blood pressure Control mm Hg | Response | Δ % | Left atrial pressure Control | Response | Δ % |
|---|---|---|---|---|---|---|---|
| 2.5 | 3 | 80.0<br>± 2.9 | 76.7<br>± 2.7 | - 4.1<br>± 2.5 | 3.7<br>± 0.4 | 4.1<br>± 0.8 | 10.8<br>± 1.0 |
| 5.0 | 3 | 80.7<br>± 0.7 | 61.3[a]<br>± 9.3 | -23.8<br>± 7.0 | 3.8<br>± 0.4 | 4.9<br>± 1.0 | 37.2<br>± 7.2 |

| CFC-113 % Inhaled Concentration | Monkey # | Pulmonary arterial pressure (mm Hg) Control | Response | Δ % |
|---|---|---|---|---|
| 2.5 | 3 | 9.0<br>0.0 | 9.2<br>± 0.4 | + 3.3 Mean<br>± 4.2 S.E.M. |
| 5.0 | 3 | 9.5<br>± 0.3 | 9.6<br>± 0.2 | + 1.1 Mean<br>± 1.1 S.E.M. |

[a] $p < 0.05$ compared with control

Data from Belej et al. (1974)

TABLE 5-5. RESPIRATORY AND CIRCULATORY EFFECTS OF CFC-113 UPON ANESTHETIZED RHESUS MONKEYS (BASED ON STUDY BY AVIADO AND SMITH)

| % Concentration CFC-113 | Monkey # | Pulmonary resistance Control cm $H_2O$/l/sec | Response | % Δ | Pulmonary compliance Control µl/cm $H_2O$ | Response | % Δ |
|---|---|---|---|---|---|---|---|
| 2.5 | 3 | 21.78 ± 3.49 | 19.69 ± 2.71 | - 8.87 + 4.75 | 6.87 ± 0.43 | 7.27 ± 0.41 | + 5.97 ± 2.30 |
| 5.0 | 3 | 21.58 ± 3.00 | 18.84 ± 2.47 | -12.07 ± 6.64 | 6.67 ± 0.58 | 7.50 ± 0.25 | ±13.95 ± 8.80 |

| % Concentration CFC-113 | Monkey # | Respiratory minute Control ml/min. | Response | % Δ | Heart rate Control bpm | Response | % Δ |
|---|---|---|---|---|---|---|---|
| 2.5 | 3 | 1230 47.3 | 1250 ± 28.9 | + 1.80 ± 1.80 | 169 ± 13.65 | 199 ± 19.09 | +18.07 ± 8.14 |
| 5.0 | 3 | 1292 ± 99 | 1302 ± 72 | + 1.10 ± 3.20 | 173.33 ± 12.02 | 221.67 ±21.67 | +27.85[a] + 8.58 |

| % Concentration CFC-113 | Monkey # | Aortic blood pressure Control mm Hg | Response | % Δ |
|---|---|---|---|---|
| 2.5 | 3 | 101.67 ± 1.67 | 93.00 ± 3.05 | - 8.54[a] ± 2.36 |
| 5.0 | 3 | 110.67 ± 5.78 | 82.33 ± 2.33 | -25.15[a] ± 4.75 |

[a] $p < 0.05$

Data from Aviado and Smith (1975).

respiratory minute volume, a significant increase in heart rate for the group that inhaled 5.0 percent (50,000 ppm; 385,000 mg/m$^3$) CFC-113, and a significant decrease in aortic blood pressure for both groups.

5.1.3 Neurological Effects

5.1.3.1 Frog--Young and Parker (1975) studied the effect of CFC-113 on the activity of acetylcholinesterase, an enzyme required in the repolarization of nerve fibers. A vagal heart preparation of the leopard frog (Rana pipiens) was used. The heart was stimulated by a pair of platinum electrodes and was triply cannulated to allow for the introduction of the test compound. The specifics of the experimental procedure were not given.

Their results indicated that the $ED_{50}$ for a CFC-113-induced increase in acetylcholinesterase activity was $1.6 \times 10^{-4}$ gm/ml, a level close to its saturation concentration in water.

5.1.3.2 Dog--Carter et al. (1970) studied the effects of CFC-113 on neural transmission through autonomic ganglia. Spinal preparations of four female beagle dogs (8.0-13.7 kg) were tested using heart rate as an indicator of the cardiac response to pre- and postganglionic stimulation. Control responses were determined prior to the administration of 2 percent (20,000 ppm; 154,000 mg/m$^3$) CFC-113 with and without atropine (0.05 mg/kg). The experimental values were determined at the end of the ten-minute exposure period. The control values were then verified 15 minutes after the termination of the exposure. Approximately two percent (20,000 ppm; 154,000 mg/m$^3$) CFC-113 had no effect upon postganglionic stimulation, although it did reduce an increase in the heart rate response to preganglionic stimulation and further decreased it when atropine was added. The authors believe that the further decrease in response in the presence of atropine, a muscarinic blocking agent, could be indicative of CFC-113-induced nicotinic blockade in the stellate ganglion.

Neurochemical effects in rats exposed to 1,000 and 2,000 ppm (7,700 and 15,400 mg/m$^3$) CFC-113 are described on page 4-3 and 4-4.

5.1.4 Hepatotoxicity

Proliferation and vacuolization of the smooth endoplasmic reticulum of the liver was observed when male Wistar rats were exposed to 1,000 and 2,000 ppm (7,700 and 15,400 mg/m$^3$) CFC-113 for 1 and 2 weeks (Vainio et al., 1980). The rough endoplasmic reticulum showed no clear alteration. Observations were made by electron microscopy. Hepatocyte microvilli were normal while some mitochondria showed condensations. No effects of exposure to 200 ppm (1,540 mg/m$^3$) were noted. Effects of CFC-113 exposure on hepatic enzymes are discussed in Chapter 4.

The exposure phase of a 90-day and two-year inhalation study in rats, conducted for Allied Corporation and E.I. Dupont de Nemours and Company, has been completed. It was reported that the gross and microscopic pathology evaluation on the 90-day study and on the one-year interim sacrifice(s) of the two-year study show no evidence of toxicity at concentrations as high as 20,000 ppm (154,000 mg/$m^3$) (E.I. duPont de Nemours and Company, 1983). Final assessment of the two-year exposures is underway and will be completed in 1983.

5.1.5 Teratogenic Effects

The following discussion subscribes to the basic viewpoints and definitions of the terms "teratogenic" and "fetotoxic" as summarized by the Office of Pesticides and Toxic Substances (U.S. EPA, 1980) as follows:

Generally, the term "teratogenic" is defined as the tendency to produce physical and/or functional defects in offspring in utero. The term "fetotoxic" has traditionally been used to describe a wide variety of embryonic and/or fetal divergences from the normal which cannot be classified as gross terata (birth defects) -- or which are of unknown or doubtful significance. Types of effects which fall under the very broad category of fetotoxic effects are: death, reductions in fetal weight, enlarged renal pelvis edema, and increased incidence of supernumerary ribs. It should be emphasized, however, that the phenomena of terata and fetal toxicity as currently defined are not separable into precise categories. Rather, the spectrum of adverse embryonic/fetal effects is continuous, and all deviations from the normal must be considered as examples of developmental toxicity. Gross morphological terata represent but one aspect of this spectrum, and while the significance of such structural changes is more readily evaluated, such effects are not necessarily more serious than certain effects which are ordinarily classified as fetotoxic--fetal death being the most obvious example.

In view of the spectrum of effects at issue, the Agency suggests that it might be useful to consider developmental toxicity in terms of three basic subcategories. The first subcategory would be embryo or fetal lethality. This is, of course, an irreversible effect and may occur with or without the occurrence of gross terata. The second subcategory would be teratogenesis and would encompass those changes (structural and/or functional) which are induced prenatally, and which are irreversible. Teratogenesis includes structural defects apparent in the fetus, functional deficits which may become apparent only after birth, and any other long-term effects (such as carcinogenicity) which are attributable to in utero exposure. The third category would be embryo or fetal toxicity as comprised of those effects which are potentially reversible. This subcategory would therefore include such effects as weight reductions, reduction in the degree of skeletal ossification, and delays in organ maturation.

Two major problems with a definitional scheme of this nature must be pointed out, however. The first is that the reversibility of any phenomenon is extremely difficult to prove. An organ such as the kidney, for example, may be delayed in development and then appear to "catch up." Unless a series of specific kidney function tests are performed on the neonate, however, no conclusion may be drawn concerning permanent organ function changes. This same uncertainty as to possible long-lasting aftereffects from developmental deviations is true for all examples of fetotoxicity. The second problem is

that the reversible nature of an embryonic/ fetal effect in one species might, under a given agent, react in another species in a more serious and irreversible manner.

The teratogenic potential of CFC-113 was recently evaluated in rats by Imperial Chemical Industries (Ward, 1983). In the summary, it is stated:

> Groups of twenty-four pregnant rats were exposed to 5,000, 12,500, and 25,000 ppm ARCTON* 113 in air for six hours per day on days 6-15 (inclusive) of gestation. A concurrent control group was exposed to air only.
>
> A reduction in maternal bodyweight gain, food utilization and food consumption occurred in the 25,000 ppm group compared with controls. Signs of hyperactivity were seen in the 25,000 ppm group during exposure but there were no macroscopic abnormalities at autopsy in this group or in the 12,500 or 5,000 ppm groups, which could be attributed to ARCTON* 113.
>
> There was no evidence of embryotoxicity which could be related to exposure to ARCTON* 113. The only increase in fetal abnormalities was the incidence of extra ribs at all exposure levels, but the incidences were within the background control range. Therefore, ARCTON* 113 is not teratogenic in rats at the exposure concentrations used in this investigation.

Two unpublished studies in rabbits are available from E.I. DuPont de Nemours and Company, Inc. (Hazelton Laboratories, 1967). In both studies, the number of pregnant animals and fetuses evaluated was inadequate for use in assessing the teratogenic potential of CFC-113. In both studies, the treatment period was shorter than those suggested for current teratogenicity testing. In both the inhalation and feeding studies, dosages administered produced signs of maternal toxicity.

The first study, performed in 1967, exposed 12 rabbits per dosage group via inhalation to 0 (air), 2,000 or 20,000 ppm (15,400 or 154,000 $mg/m^3$) of CFC-113 for 2 hours daily on days 8 through 16 of presumed gestation (equivalent to days 6 through 14 of gestation when day 0 = day of insemination). Pregnancy occurred in 4, 4 and 7 rabbits in the respective dosage groups. Signs of maternal toxicity in rabbits exposed to 20,000 ppm (154,000 $mg/m^3$) of CFC-113 consisted of lowered body weight gain during the first week of exposure, and eye irritation. One doe in the 20,000 ppm (154,000 $mg/m^3$) dosage group died; another delivered prematurely on day 29.

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*ARCTON is the trademark used by Imperial Chemical Industries for their fluorocarbon products.

A total of 19/4 (pups/litter), 8/4 (pups/litters), and 24/5 (pups/litters) was evaluated in the control, low and high dosage groups, respectively. One pup in the low and two in the high dosage group were dead at examination. No remarkable variations were observed in external soft tissue or skeletal examinations of the fetuses.

The second study, performed in 1967, evaluated 8 rabbits per dosage group, and 0 (distilled water), 1 and 5 gm/kg/day CFC-113 were administered orally by stomach tube on days 8 through 11 of gestation (gestation day 0 was the second day of mating). One, 3 and 4 rabbits died in the groups administered 0, 1 and 5 gm/kg/day CFC-113, respectively. In high dosage group rabbits, food and water consumption were reduced during the treatment period, and body weight loss (300 to 500 grams) occurred. Only 3, 6 and 4 rabbits in the respective dosage groups became pregnant. The three control rabbits delivered naturally 21 live and 3 dead pups.

In low dosage group rabbits, one of the pregnant rabbits died following the third dose, another died during natural delivery, and the third rabbit survived to deliver pups. The remaining three rabbits in the lowest dosage groups that were pregnant were Caesarean-sectioned. A total of 32 live fetuses or pups was evaluated.

Death in one rabbit in the high dosage group after the first dose precluded evaluation for pregnancy in one rabbit. One rabbit died after the fourth dose and apparently had 9 live embryos in utero. One rabbit died on day 16 (day 14 when day 0 = insemination) of gestation and had nine dead fetuses in utero. Another rabbit aborted four dead fetuses on day 29 (day 27 when day 0 = insemination) of gestation. One rabbit was Caesarean-sectioned and had 10 fetuses in utero, 7 of which were dead.

As a result of non-pregnancy, maternal death or in utero embryo/fetal death, only 21/3 (pups/litters), 32/5 (pups/litters), and 3/1 (pups/litters) delivered naturally or Caesarean delivered were evaluated for malformations. Eleven dead fetuses in two litters, either aborted or dead in utero, were also evaluated for malformations. No remarkable anatomical changes were reported in the fetuses which were examined.

5.1.6 Mutagenic Effects

5.1.6.1 Mouse--Using a dominant lethal assay, Epstein et al. (1972) tested the mutagenic effects of CFC-113. Swiss mice (8-10 week old males and virgin females) were used. The following criteria for determining mutagenicity were used: "(1) one or more weeks with a mean of 0.90 or more early fetal deaths per

pregnancy regardless of the percent of pregnant females with early deaths; (2) one or more weeks with 55 percent or more of the pregnant females having early deaths; (3) one or more weeks with a mean of less than 9 total implants per pregnancy." There were two experimental groups of males injected i.p. with CFC-113: group 1, 200 mg/kg (7 mice); group 2, 1000 mg/kg (9 mice). Each male was subsequently caged with three virgin females which were replaced weekly for eight weeks. The females were sacrificed and autopsied thirteen days after the midweek of the caging.

Neither experimental group met the above criteria. The authors concluded that CFC-113 was not mutagenic under the concentrations tested, or under the route of administration, strain and test system employed.

CFC-113 was tested in four strains (TA 1535, 1537, 98 and 100) in the S. typhimurium microsome test (Haskell Laboratory, unpublished, 1977). CFC-113 were reported to be negative because the reversion frequency was less than two times the spontaneous frequency and because less than 0.02 revertants/ nmole was observed. Negative responses were obtained both in the presence and absence of a rat-liver homogenate activation system. The experiment was carried out in 9-liter glass chambers with CFC-113 in air at concentrations of 2 percent, 6 percent, 10 percent, and 19 percent by volume. Chloroethylene served as the positive control. The cytotoxicity of the test sample in the presence and absence of an activation system as measured in TA 1535 was the basis for selective concentrations for mutagenesis testing.

The negative results obtained from the dominant lethal test and the Salmonella/mammalian microsome test are too limited to provide sufficient evidence to classify CFC-113 as non-mutagenic. Furthermore, the dominant lethal test is not considered to be a sensitive test because of the high background of spontaneously-occurring dominant lethals (Russell and Matter, 1980). Additional tests are needed before a conclusive determination of the mutagenic potential of CFC-113 can be made.

5.1.7 Carcinogenic Effects

5.1.7.1 Rat--A two-year chronic inhalation study in rats at exposure levels of 2,000; 10,000; and 20,000 ppm (15,400; 77,700; 155,400 $mg/m^3$) has been completed recently by Haskell Laboratories. Although histopathological evaluations are still in progress, preliminary data indicate no gross pathological effects attributable to CFC-113 except decreased weight gain at 20,000 ppm (154,000 $mg/m^3$) (E.I. duPont de Nemours and Company, 1983).

5.1.7.2 Mouse--The use of sprays containing a pesticide, a piperonyl synergist and a solvent prompted Epstein and coworkers (1967a) to evaluate the

potential of CFC-113 to potentiate the action of piperonyl butoxide (PB), a pesticide synergist. Incidences of hepatomas and lymphomas were used to indicate carcinogenicity. The number of mice and litters in each of the four test groups presented in Tables 5-6 and 5-7 is indicated in Table 5-7. Each group received the following subcutaneous injections into the neck: 0.1 ml on days 1 and 4 and 0.2 ml on days 14 and 21 after birth. The groups were differentiated according to the solution injected (each group was injected subcutaneously with test material): (1) solvent controls (redistilled tricaprylin); (2) 10 percent (100,000 ppm; $7.7 \times 10^5$ mg/m$^3$) CFC-113 in tricaprylin; (3) 5 percent PB in tricaprylin; (4) CFC-113 and PB as indicated in (2) and (3).

The data are presented in Table 5-6. They indicate that 10 percent (100,000 ppm; $7.7 \times 10^5$ mg/m$^3$) CFC-113 did not alter the incidence of hepatomas or the incidence of malignant lymphomas beyond the control values. One case of a mammary carcinoma was also found among the females of group two. No mammary carcinomas were found in the control group. It is important to note that the statistical significance of these data was not evaluated.

Conney et al. (1972) reported that environmental exposure to piperonyl butoxide is unlikely to inhibit human microsomal enzyme function.

5.1.8 Synergistic Effects

Epstein et al. (1967a, 1967b) tested the potential of CFC-113 to potentiate the action of piperonyl butoxide (PB) upon neonatal Swiss mice. Percent mortality prior to weaning was used to indicate the effects of CFC-113 and PB alone or in combination. This study was part of the study discussed previously.

Table 5-7 suggests a synergistic effect between CFC-113 and PB. The mortality rate of CFC-113 + PB (46 percent) was greater than either compound alone (2 percent and 15 percent). The data in Table 5-6 do not permit conclusions on the synergistic hepatotoxicity or synergistic lymphotoxicity of CFC-113 and PB.

5.1.9 Dermal Effects

Table 5-8 summarizes the data found on the dermal effects of CFC-113 in mammals. Few effects have been observed, other than a drying of the skin due to lipid removal.

5.1.10 Inhalation and Ingestion

A variety of acute and subchronic inhalation exposures of rodent species to levels of CFC-113 ranging from 2,000 to 400,000 ppm (15,400 to $3.1 \times 10^{-6}$ mg/m$^3$) has been reported. The spectrum of effects observed ranges from reported

TABLE 5-6. CARCINOGENIC EFFECTS OF PIPERONYL BUTOXIDE IN COMBINATION WITH CFC-113 IN MICE, ALONE AND IN COMBINATION

| Treatment group | Sex | # of mice autopsied, alive at week 51 (# at risk) | Hepatomas # of tumors in each period as % of # of mice at risk (number) | Hepatomas # of tumors in each period as % of # of mice at risk (percent) | Malignant lymphomas # of tumors in each period as % of # of mice at risk (number) | Malignant lymphomas # of tumors in each period as % of # of mice at risk (percent) |
|---|---|---|---|---|---|---|
| Solvent controls | M | 48 | 4 | 8 | 1 | 2 |
| | F | 68 | 0 | 0 | 0 | 0 |
| CFC-113 | M | 21 | 1 | 5 | 0 | 0 |
| | F | 20 | 0 | 0 | 1 | 5 |
| PB | M | 20 | 0 | 0 | 0 | 0 |
| | F | 36 | 0 | 0 | 0 | 0 |
| CFC-113 and PB | M | 18 | 3 | 17 | 0 | 0 |
| | F | 24 | 0 | 0 | 1 | 4 |

In addition, one mammary carcinoma occurred in one female of the CFC-113 alone group.

Data from Epstein et al. (1967a).

TABLE 5-7. SYNERGISTIC EFFECT OF PIPERONYL BUTOXIDE IN COMBINATION WITH CFC-113 UPON NEONATAL MICE

| Treatment group | # of mice (# of litters) | Weaning mortality | Average wt. (g) at 51 weeks | % Increase in weight over controls |
|---|---|---|---|---|
| Solvent controls | 170 (16) | 14 | M 50.5<br>F 45.3 | |
| 10% CFC-113 | 52 (4) | 2 | M 53.6<br>F 48.2 | 6.1<br>6.4 |
| 5% PB | 91 (8) | 15 | M 52.0<br>F 47.0 | 3.0<br>3.8 |
| 10% CFC-113 + 5% PB | 94 (8) | 46 | M 59.0<br>F 57.0 | 16.8<br>25.8 |

Data from Epstein (1967a).

TABLE 5-8. DERMAL EFFECTS OF CFC-113 IN MAMMALS

| Concentration | Duration | Effects | Reference |
|---|---|---|---|
| 40% in sesame seed oil | daily, 12 days | No effect on shaved skin of rabbits | U.S. EPA, 1976 |
| 100% | 5 x/w, 20 w | No visible effect on shaved back of rabbits | Desoille et al., 1968 |
| 100% | | Practically non-irritating to eye and paw of rabbit | Duprat et al. 1976 |
| 5 g/kg | 1 x/d, 5 d | Weight fluctuations, skin damage, liver changes (microscopic), no other systemic effects in rabbits | Desoille et al., 1968 |
| >11 g/kg | | Largest feasible dose (rats). Dermal and tissue damage at site of application; no other systemic effects in rats. No deaths | Clayton, 1966 |

no effect/slight narcotic effects (up to about 50,000 ppm; 385,000 $mg/m^3$) to anesthesia and ensuing death, at an approximate dose level of 100,000 ppm (770,000 $mg/m^3$).

Due to the amount and diversity of data on CFC-113, this information is presented in tabular form (Table 5-9).

TABLE 5-9. INHALATION AND INGESTION TOXICITIES OF CFC-113 IN MAMMALS

| Animal (Number) | % | ppm | A/S* | Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| Mice | 5.7 | 57,000 | A | 30 min | Anesthetic; delayed death with >6% | Raventos and Lemon, 1965 |
| | 5-12 | 50,000-120,000 | A | 15 min | Initial excitement and convulsions during anesthesia | Burn, 1959 |
| | 9.5 | 95,000 | A | 2 hr | $LC_{50}$ | Desoille et al., 1968 |
| | >10 | >100,000 | A | 30 min | $LC_{50}$ | Raventos and Lemon, 1965 |
| (40♂) | 0.2 | 2,000 | S | 2 w | Hematological values; clinical chemistries; EEG; body weight; organ-to-body weight ratios: no change | Carter et al., 1970 |
| Guinea Pigs | | | | | | |
| (12) | 1.0 to | 10,000 to | A | 5 min | No adverse effects; recovered quickly | Underwriters' Laboratories, 1941 |
| (9) | 1.2 | 12,000 | A | ½ hr | Same | |
| (6) | | (51% humidity, | A | 1 hr | Same | |
| (3) | | 58°F) | A | 2 hr | Same | |
| | 1.1 | 11,000 | A | 2 hr | Slight narcotic effect | AIHAC, 1968 |

TABLE 5-9. (continued)

| Animal (Number) | % | ppm | A/S* | Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| Guinea Pigs | | | | | | |
| (12) | 2.5 to 2.9 | 25,000 to 29,000 | A | 5 min | No adverse effects; recovered quickly | Underwriters' Laboratories, 1941 |
| (9) | | (41% humidity; 67-68°F) | A | ½ hr | Slight tremors within 10'; rapid breathing; eyes partially closed; slight lachrymation; recovered quickly | |
| (6) | | | A | 1 hr | Same | |
| (3) | | | A | 2 hr | Same; recovered within 2 days | |
| (12) | 4.8 to 5.2 | 48,000 to 52,000 | A | 5 min | No adverse effects; recovered quickly | Underwriters' Laboratories, 1941 |
| (9) | | (67% humidity; 68-70°F) | A | ½ hr | Coordination loss; tremors; unable to stand within 10'; irregular breathing; eyes partially closed; lachrymation; recovered within one day | |
| (6) | | | A | 1 hr | Semi-conscious; convulsive tremors; irregular breathing; deaths of 2 animals 4 and 5 days post-exposure; recovery within 8 days | |
| (3) | | | A | 2 hr | Same; deaths 2 and 3 days post-exposure | |
| (12) | 9.5 to 11.3 | 95,000 to 113,000 | A A A | 5 min | Coordination loss; tremors; unable to stand; recovery within 1 day | Underwriters' Laboratories, 1941 |
| (9) | | (51% humidity; 70-72°F) | A | ½ hr | Unconscious; convulsive tremors; lachrymation and nasal discharge; breathing fast and irregular; death of 2 animals 3 and 4 days post-exposure | |

TABLE 5-9. (continued)

| Animal (Number) | % | ppm | A/S* | Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| Guinea Pigs (6) | | | A | 1 hr | Same; deaths 1 and 4 days post-exposure | |
| (3) | | | A | 2 hr | Same; all animals dead within 1 day post-exposure | |
| Hartley albinos | 12 | 120,000 | A | 2 hr | $LC_{50}$ | Desoille et al., 1968 |
| (12) | 16.4 to 16.6 | 164,000 to 166,000 | A | 5 min | Coordination loss within 1'; unable to stand; convulsive tremors; recovered within 1 day | Underwriters' Laboratories, 1941 |
| (9) | | | A | ½ hr | Unconscious; convulsive tremors; deaths; 5 animals within first 20'; 2 animals 1 and 2 days post-exposure | |
| (2) | | (73°F) | A | 1 hr | Unconscious; deaths: 1 animal within first 45'; 1 animal 2 days post-exposure | |
| (10♀) | 0.51 | 5,100 | S | 6 hr/day 5 day/wk 4 wk | No change in growth rate, organ-to-body weight ratios, appearance upon necropsy | Steinberg et al., 1969 |
| (3) | 2.5 | 25,000 | S | 3.5 hr/day 20 days | 0/3 deaths; no changes in weight gain, rbc, wbc, differential white count, hemoglobin, urinary protein and sediment, heart, lungs, liver, kidney, spleen; no signs of toxicity | Clayton, 1966 |
| Rats (5♂) | 1.14 | 11,400 | A | 6 hr | Rotobar performance: no change | Steinberg et al., 1969 |
| (5♂) | 1.3 | 13,000 | A | 6 hr | 1 h: restlessness<br>2 h: quiet; rotobar test, no change | |

TABLE 5-9. (continued)

| Animal (Number) | % | ppm | A/S* | Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| | 1.76 | 17,600 | A | 2 hr | Liver and kidney congestion | AIHAC, 1968 |
| | 5.5 | 55,000 | A | 4 hr | ALC | U.S. EPA, 1966 |
| | 8.7 | 87,000 | A | 6 hr | Convulsions;unresponsiveness; respiratory impairment; microscopic exam: pulmonary edema; ALC | Clayton, 1962 |
| | 10.0 | 100,000 | A | 3 hr | Convulsions, rapid breathing, unresponsiveness, cyanosis, death in 2-3 hrs | AIHAC, 1968 |
| (5♂) | 10.0 | 100,000 | A | 6 hr | ALC | Clayton, 1966 |
| Wistar albinos | 11 | 110,000 | A | 2 hr | $LC_{50}$; some delayed mortality | Desoille et al., 1968 |
| | 15 | 150,000 | A | 15 min | Anesthetic | Kuebler, 1964 |
| | 20 | 200,000 | A | 45 min | ALC | U.S. EPA, 1966 |
| | 22.2 | 222,000 | A | | 3-15': convulsions, rapid breathing, unresponsiveness, cyanosis, death | AIHAC, 1968 |
| (10♂ and 10♀) | 0.21 to 0.29 | 2,075 to 2,885 | S | 7 hr/day 30 days | 0/20 deaths; body weights, gross and microscopic pathology: normal; no signs of toxicity | Clayton, 1966 |
| Rats (5♂) | 0.2 | 2,000 | S | 2 wk | 0/5 deaths; hematological values, clinical chemistries, EEG, body weight, organ-to-body weight ratios: no changes except in kidneys (wt >controls), no adverse symptomology | Carter et al., 1970 |
| (20) | 0.2 | 2,000 | S | 2 wk | See Table 10 | Clayton, 1962 |
| | 0.5 | 5,000 | S | 7 hr/day 5 day/wk 30 days | No deaths, no weight gain, slight liver damage | |
| (12) | 0.5 | 5,000 | S | 7 hr/day 30 days | 0/12 deaths, abnormal weight gain; 3 rats: slightly pale livers, others normal; kidneys normal | Clayton, 1966 |

TABLE 5-9. (continued)

| Animal (Number) | % | ppm | A/S* | Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| (50♂) | 0.51 | 5,100 | S | 6 hr/day 5 day/wk 4 wk | Rotobar test: no change | Steinberg et al., 1969 |
| (5♂) | 0.51 | 5,100 | S | 6 hr/day 5 day/wk 4 wk | Voluntary movement (activity wheels) and necropsy: no changes | Steinberg et al., 1969 |
| (10♀ and 10♂) | 0.51 | 5,100 | S | 6 hr/day 5 day/wk 4 wk | Growth rate, organ-to-body weights, necropsy: no changes | |
| (5♂) | 2.5 | 25,000 | S | 3.5 hr/day 20 days | 0/5 deaths; weight gain, rbc, wbc, differential white count, hemoglobin, urinary protein and sediment, heart, lungs, liver, kidney, spleen: no changes; no signs of toxicity | Clayton, 1966 |
| Rats (5) | 6 | 60,000 | S | 1 hr/day 5 days | Deaths: 0/5; liver: 2 rats fair amounts of fat in Kupffer cells | Burn et al., 1959 |
| (4) | 40 | 400,000 | S | 1 hr/day 5 days | Deaths: 0/4; mild hepato-toxicity; moderate degree of mitotic activity in liver cells of one rat; others showed similar activity but to a lesser degree | |
| Wistar albinos | 1.2 | 12,000 | C | 2 hr/day 5 day/wk, 365-730 days | Deaths: 3/6 (3/6 Controls died also); sleepiness | Desoille et al., 1968 |
| Sprague-Dawley (5♂) | | 30 g/kg | I | undiluted dosed orally, 1x | 0/5 deaths; lethargy; facial edema; abdominal distension; liquid fecal discharge: symptoms disappeared after 24 h; ruffled coat; autopsies: no gross pathological changes; avg wt. change: +46 g | Michaelson and Huntsman, 1964 |

TABLE 5-9. (continued)

| Animal (Number) | % | ppm | A/S* | Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| (5♂) | | 35 g/kg | I | Same | Same; avg. wt change: +41 g | |
| (5♂) | | 50 g/kg | I | Same | Same; avg wt. change: +19 g | |
| (5♂) | | 43 g/kg | I | Undiluted dosed orally, 1x | 43 ± 4.8 g/kg = $LD_{50}$ | Michaelson and Huntsman, 1964 |
| (5♂) | | 45 g/kg | I | Same | Lethargy; facial edema; abdominal distension; liquid fecal discharge: symptoms disappeared after 24 h; ruffled coat; deaths: 3/5, 5-24 hr post-ingestion; avg wt. change of survivors +25 g; avg wt. change of dead animals: -12g; autopsy of dead animals: lung hemorrhaging, possibly due to contact with CFC-113; livers: mottled surface, normal color; stomach and GI tract: abnormally distended with gas and fluid | Michaelson and Huntsman, 1964 |
| | | 45 g/kg | I | | ALC | Clayton, 1966 |
| (5♂) | | 50 g/kg | I | Undiluted dosed orally, 1x | Same effects as 45 g/kg; deaths: 4/5, days 1-7 post-exposure; avg. wt. change survivors: 31 g; avg. dead animals: -49 g | Michaelson and Huntsman, 1964 |
| (5♂) | | 55 g/kg | I | Same | Same; deaths: 5/5, days 3-9 post-exposure; avg. wt. change: 0 g | |
| Rabbits, albino | 1.1 | 11,000 | S | 2 hr/day 5 day/wk 120 wk | Deaths: 0/6; no variation | Desoille et al., 1968 |
| | | 17 g/kg | I | | Approximate lethal dose | AIHAC, 1968 |

TABLE 5-9. (continued)

| Animal (Number) | % | ppm | A/S* | Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| Dogs (2♀ and 2♂) | 1.14 | 11,400 | A | 6 hr | 2 hr: vomiting, lethargy, nervousness; 4 hr: stupor, lethargy; 5-6 hr: tremors; 15 minutes post-exposure: no signs | Steinberg et al., 1969 |
| Dogs (1♂ and 1♀) | 1.3 | 13,000 | A | 6 hr | 5 min: depressed placing reflex; 10 min: nervousness; 15': extreme pupil dilation, trembling; 30min: loss of muscle coordination; 1 hr: vomiting, trembling; 5 min. post-exposure: depressed front and rear hopping reflex; 15 min. post-exposure: no signs | Steinberg et al., 1969 |
| (8♂) | 0.2 | 2,000 | S | 2 wk | Hematological values; clinical chemistries; EEG; body weight; organ-to-body weight ratios: no changes; 0/8 deaths | Carter et al., 1970 |
| (2♂ and 2♂) | 0.51 | 5,100 | S | 6 hr/day 5 day/wk 4 wk | Plasma LDH, amylase activity, BUN, hematocrit, % neutrophils, % lymphocytes checked weekly: no changes; organ-to-body weight ratios, food consumption, olfactory, hearing, following with eyes; blinking, facial skin sensation, tone of face and jaw muscles, gag reflex, tongue control, light-pupillary reflex, optic disc appearance, flexor, extensor postural thrust, placing, righting, hopping, knee jerk: no changes; no pathological changes | Steinberg et al., 1969 |
| (2) | 1.25 | 12,500 | S | 3.5 hr/day 20 days | 0/2 deaths; weight gain, rbc, wbc, differential white count, hemoglobin, urinary protein and sediment, heart, lungs, liver, kidney, spleen: all normal; no signs of toxicity | Clayton, 1966 |

TABLE 5-9. (continued)

| Animal (Number) | % | ppm | A/S* | Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| Dogs | | | | | | |
| (1♀ and 1♂) | | 200 ml. into exposed stomach | | 2 hr | Stomach exposed, cardiac and pyloric sphincters ligated, CFC-113 added; 2 h: gastric juices measured; volume = 200 ml.; gross appearance gastric mucosa: normal | Clayton, 1966 |
| (2) | 1.25 | 12,500 | S | 3.5 hr/day 20 days | 0/2 deaths; weight gain, rbc, wbc, differential white count, hemoglobin, urinary protein and sediment, heart, lungs, liver, kidney, spleen: all normal; no signs of toxicity | Ibid. |
| Monkeys | | | | | | |
| (4♀) | 0.2 | 2,000 | S | 2 wk | 0/4 deaths; hematological values, clinical chemistries, EEG, body weight: no changes; organ-to-body weight ratios: all monkeys, enlarged thyroids; control: monkeys: all thyroids normal | Carter et al., 1970 |

*I = Ingested; A = acute; S = Subchronic; C = Chronic

## 5.2 HUMAN STUDIES

Much of what is known is derived from instances in which individuals were accidentally or experimentally exposed to high concentrations of chlorofluorocarbons.

### 5.2.1 Occupational Exposure Studies

Triebig and Burkhardt (1978) observed the effects of occupational inhalation exposures to CFC-113. Ten women (25-54 years of age; length of exposure 1-14 years, average 8.7 years) and three men (27-43 years of age; length of exposure 6-21 years, average 11 years) were used in the study. Case histories, clinical chemistry (blood Hb, $Hb_E$, erythrocytes, leukocytes, SGOT, SGPT, fasting blood sugar, urine protein, sugar, bile pigment, and sedimentation rate), and breath analyses were performed before the one-week exposure period. After the exposure period, blood chemistry, urinalysis, and breath analyses were performed again. The concentration of CFC-113 in the workroom was determined by infrared spectrometry. Room air measurements indicated average daily levels between 23.3 ± 9.2 and 62.4 ± 29.5 ppm (180 ± 71 and 480 ± 227 $mg/m^3$) during the exposure period. Prior to the commencement of this experiment, each of the women had worked at least one day in the workroom (concentration CFC-113, 11 to 113 ppm; 85 to 870 $mg/m^3$) and each of the men had worked 15 to 20 minutes/day for 2 to 3 days/week. During the one week observation period, each woman spent one day in the workroom (3.5 to 5.8 hours) while the men had irregular and brief periods of exposure. Analysis of blood and urine revealed no abnormalities. At the end of the daily exposure, breath analyses indicated a range of 1.0 to 33.8 ppm (7.7 to 260 $mg/m^3$) CFC-113 in the women.

Imbus and Adkins (1972) also conducted studies of the effects of occupational exposures to CFC-113. Only males were observed. Clinical examination and blood chemistry (cholesterol, calcium, inorganic phosphorus, total bilirubin, albumin, total protein, uric acid, BUN, glucose, lactate dehydrogenase, alkaline phosphatase, and SGOT) were used as an indication of adverse effects. There were fifty males in each of the two groups: (1) those unexposed to CFC-113 (average age 37 years); (2) those exposed to CFC-113 (average age 34 years; average exposure 2.77 years; exposure values determined from one day's 161 samplings: range 46 to 4,780 ppm (354 to 36,806 $mg/m^3$), mean 699 ppm (5,382 $mg/m^3$), 50th percentile estimate 521 ppm (4,012 $mg/m^3$), median 425 ppm (3,272 $mg/m^3$). The results indicated no adverse effects other than one case of CFC-113-induced dermatitis.

5.2.2 Experimental Exposure Studies

5.2.2.1 Inhalation--Reinhardt et al. (1971) also conducted experiments on the effects of exposure to CFC-113 using four healthy male volunteers (22-30 years of age). A broad base of responses was measured in terms of clinical tests (equilibrium, breath analysis, chest x-ray, urinalysis, and blood chemistries: alkaline phosphatase, cholesterol, total bilirubin, total protein, albumin, globulin, A/G ratio, total lipids, SGOT, LDH, creatinine, glucose, BUN, and uric acid), psychomotor tests and subjective impressions. The subjects were exposed to CFC-113 for 3 hours in the morning and 3 hours in the afternoon, 5 days/week, for 2 weeks in an environmental chamber (6' x 6 1/2' x 10'). The concentration of CFC-113 in the environmental chamber was determined by gas chromatography. During week 1, the concentration was 500 ppm (3,850 $mg/m^3$). During week 2, the concentration was 1,000 ppm (7,700 $mg/m^3$).

Psychomotor tests were administered to each individual prior to and after exposure at each level. The authors reported no evidence of a detrimental effect due to exposure to CFC-113, based on test scores. Clinical testing, conducted before each exposure and three days after final exposure, indicated no abnormal findings regarding hematology, blood chemistry, or urinalysis. These findings were supported by no adverse subjective impressions or disturbances of equilibrium. The results of breath analyses performed after each exposure are shown in Table 5-10. As shown in Table 5-10, the morning samples obtained during the week of exposure to 1,000 ppm (7,700 $mg/m^3$) indicate that not all of the CFC-113 was eliminated overnight. Only one individual had a measurable breath level (1.5 ppm; 11.6 $mg/m^3$), about 48 hours following the last exposure to 1,000 ppm (7,700 $mg/m^3$). These data show that essentially no CFC-113 is retained by tissues 48 hours after repetitive exposures.

Stopps and McLaughlin (1967) tested the psychomotor effects of CFC-113. Two healthy males were used in the study. Four different psychomotor tests performed by each subject were used to determine adverse effects. The subjects were exposed to CFC-113 for two and three-quarter hours in an environmental chamber (2 1/2' x 3' x 5'). The timetable of the experiment is shown in Figure 5-2. The concentrations of CFC-113 in the environmental chamber were determined by gas chromatography and the concentrations tested were 1,500; 2,500; 3,500; 4,000; and 4,500 ppm (11,500; 19,250; 26,950; 30,800; and 34,650 $mg/m^3$).

TABLE 5-10. POST-INHALATION BREATH CONCENTRATIONS OF CFC-113 IN MAN

Summary of Breath Sampling Data
(Chlorofluorocarbon 113 Concentration (ppm) in Alveolar Air)

| Subject | Day of Week | Exposure | | | | Post-exposure |
|---|---|---|---|---|---|---|
| | | 500 ppm | | 1000 ppm | | |
| | | a.m. | p.m. | a.m. | p.m. | a.m. |
| I | M | < 1 | 60 | < 1 | 113 | < 1 |
| | T | < 1 | 65 | < 1 | 88 | < 1 |
| | W | < 1 | 59 | 2.0 | 71 | - |
| | T | < 1 | 57 | 1.5 | 105 | - |
| | F | < 1 | 51 | 1.5 | 93 | - |
| II | M | < 1 | 61 | < 1 | 115 | 1.5 |
| | T | < 1 | 56 | 1.5 | 85 | < 1 |
| | W | 2.0 | 51 | 1.5 | 102 | - |
| | T | < 1 | 49 | 1.0 | 79 | - |
| | F | < 1 | 55 | 1.5 | 103 | - |
| III | M | < 1 | 45 | < 1 | 88 | < 1 |
| | T | < 1 | 27 | < 1 | 66 | < 1 |
| | W | 1.5 | 18 | 2.0 | 57 | - |
| | T | < 1 | 18 | 3.0 | 54 | - |
| | F | 3.0 | 31 | 1.0 | 60 | - |
| IV | M | < 1 | 47 | < 1 | 84 | < 1 |
| | T | < 1 | 44 | 1.0 | 67 | < 1 |
| | W | < 1 | 35 | 1.5 | 56 | - |
| | T | 1.0 | 35 | 2.0 | 60 | - |
| | F | < 1 | 41 | 2.0 | 71 | - |

Note: (-) Indicates not measured (detection limit about 1 ppm).

Data of Reinhardt et al. (1971).

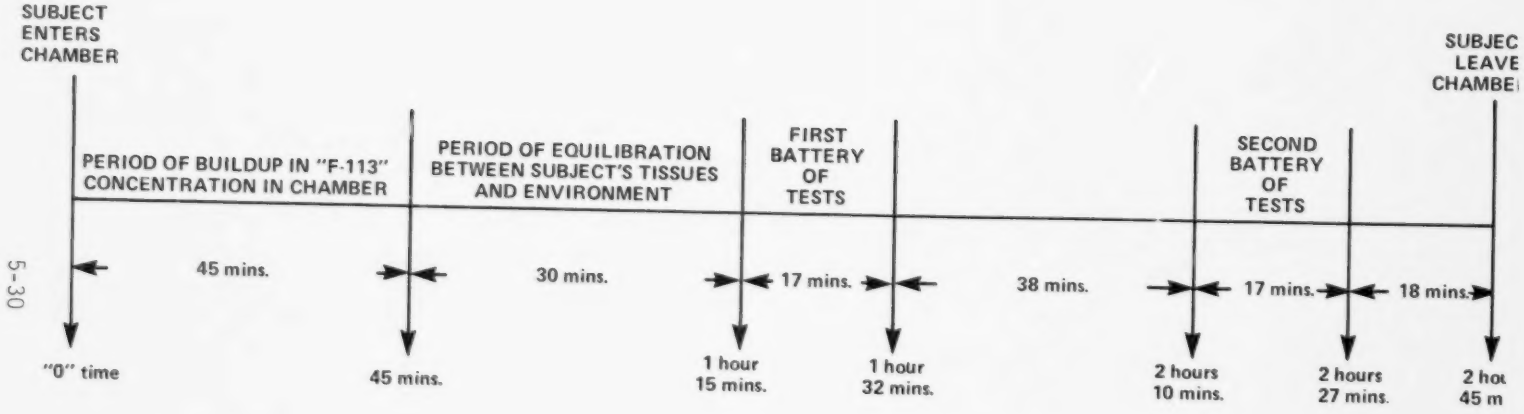


Figure 5-2. Human exposures to CFC-113; timetable of experiment.

Source: Stopps and McLaughlin (1967).

The results are presented in Figure 5-3. Because the results of the first and second series of psychomotor tests during each exposure showed no consistent trends, the scores are presented as the average of the individual scores, expressed as the percentage change from control values. The results indicate no adverse effects at 1,500 ppm (11,550 mg/$m^3$) for 2.75 hours. At concentrations of 2,500 ppm (19,250 mg/$m^3$), there was a slight but definite impairment of psychomotor performance. In addition, both subjects reported the following effects after one half to one hour exposures at the three highest concentrations tested: loss of concentration on the task at hand, drowsiness, "heaviness" in the head with no actual headache, and dizziness upon lateral shaking of the head. These effects were gone fifteen minutes after having left the chamber. Post-exposure psychomotor testing, breath and blood analyses for CFC-113 were not performed.

5.2.2.2 Ingestion--Only one report on the effects of human ingestion of CFC-113 has been found. Approximately one liter of cold CFC-113 was accidentally delivered into the stomach of an anesthetized patient, producing immediate but transient cyanosis. The patient survived and reported only severe rectal irritation and diarrhea for 3 days thereafter (Clayton, 1966).

5.2.2.3 Dermal--The results of unpublished dermatological experiments with CFC-113 conducted for E.I. duPont de Nemours and Company suggested that human scalp and forehead were not adversely affected when CFC-113 was applied over a 30-day period (Betro Research Laboratory, 1967). Twenty volunteers received applications to entire scalp and most of forehead according to the following schedule: (1) For first five days, CFC-113 was applied three times daily for 30 seconds, (2) the 6th day exposure consisted of a single 30-second application; (3) thereafter, CFC-113 was applied for 1.5 minutes, once daily. Tests included permeability, eccrine sweat secretion, sebum production, UV response, response to chemical irritants, and determination of bacterial flora.

5.2.2.4 Synergistic, Carcinogenic, Mutagenic, and Teratogenic--No information pertaining to any of these categories of effects of direct exposure to CFC-113 in man have been found.

## 5.3 SUMMARY OF ADVERSE HEALTH EFFECTS AND ASSOCIATED LOWEST OBSERVABLE EFFECTS LEVELS

Levels of CFC-113 above 2,000 ppm (15,400 mg/$m^3$) have been reported to result in cardiac sensitization of dogs only after the administration of exogenous epinephrine. No evidence of cardiac sensitization of animals in the absence of exogenous epinephrine at CFC-113 levels at or below 20,000 ppm (154,000 mg/$m^3$) has been reported.

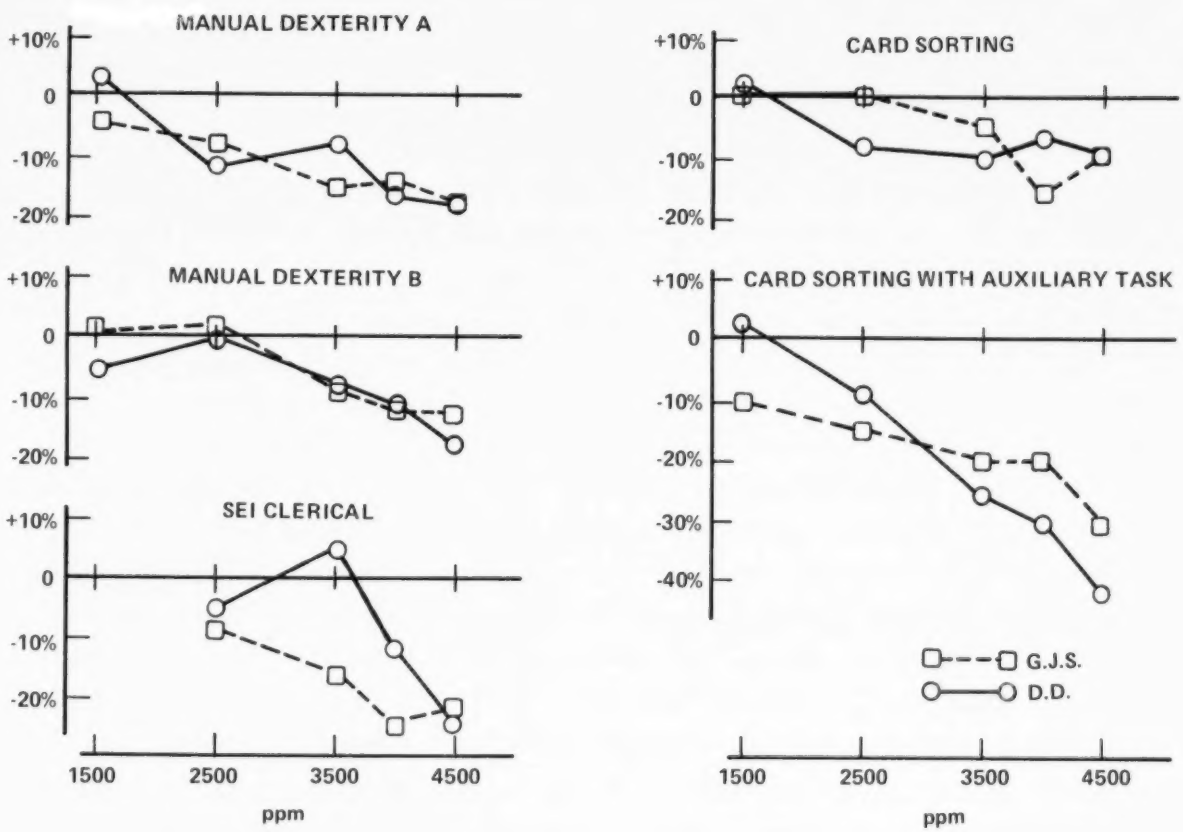


Figure 5-3. Effect of CFC-113 upon psychomotor performance in man.

Source: Stopps and McLaughlin (1967).

Animal studies with mice, rats, dogs and monkeys that had been exposed to levels exceeding 5,000 ppm (38,500 mg/$m^3$) have shown that arrhythmias, tachycardia, hypotension, and depression of myocardial contractility could be elicited.

Inhalation studies have shown that exposure to 2,000 to 19,000 ppm (15,400 to 146,300 mg/$m^3$) CFC-113 (in guinea pigs, rats, dogs, and monkeys) can result in a slight narcotic effect, liver and kidney congestion, and kidney and thyroid enlargement. Often these effects are not revealed by the usual hematological or clinical tests, indicating that these tests do not always show the full extent of changes induced by CFC-113.

No direct effect of CFC-113 exposures upon humans at ambient concentrations is known or expected. No conclusions can be drawn, at this time, with regard to the carcinogenic, mutagenic, or teratogenic potential of CFC-113.

Because of the practical limitations on the acquisition of data concerning chronic human exposure situations, it is difficult to estimate, with confidence, a lowest-observed-adverse-effect level (LOAEL) for CFC-113. The LOAEL is defined as the lowest dose in a study or group of studies producing functional impairment, behavioral abnormality, and/or pathological lesions which hinder the performance of the whole organism. Table 5-11 summarizes the results of the few presently available studies which might reasonably be used to derive an estimated LOAEL for CFC-113 at this time. Inhalation studies with animals and the acute human exposure data of Stopps and McLaughlin suggest that the LOAEL may be in the range of 2,000 to 2,500 ppm (15,400 to 19,250 mg/$m^3$). However, this level should be regarded with caution until recently-completed bioassays are comprehensively evaluated.

The data of Reinhardt et al. (1971), Triebig and Burkhardt (1978), Imbus and Adkins (1972), and Stopps and McLaughlin (1967) suggest a no-observed-adverse-effect level (NOAEL), for short-term CFC-113 exposure situations, in the range of 1,500 to 2,000 ppm (11,550 to 15,400 mg/$m^3$). The NOAEL is defined as that dose which produces observed effects which do not in themselves represent known functional impairment, behavioral abnormality, and/or pathological lesions which hinder the performance of the whole organism. The data supporting the NOAEL conclusion are shown in Table 5-12.

It should be noted that the above, tentatively-derived LOAEL and NOAEL estimates for CFC-113 are orders of magnitude higher than the highest ambient air concentrations (38.0 ppb; 0.29 mg/$m^3$) of CFC-113 encountered thus far in urban areas of the United States or elsewhere (see Table 3-2 in Chapter 3).

TABLE 5-11. LOWEST OBSERVABLE ADVERSE EFFECT LEVELS (LOAEL)

| Criteria | Species | Mode of Treatment | No. of Subjects | Duration of Exposure | Concentration (ppm) | Response | Reference |
|---|---|---|---|---|---|---|---|
| Cardiac Sensitization | beagle dog | 8 µg/kg epinephrine given i.v. prior to CFC-113 and again after exposure | 6 | 0.5 hour | 2,500 | cardiac sensitization to exogenous epinephrine (1/6) | Haskell Laboratory, 1969 |
| | | 8 µg/kg epinephrine i.v. prior to exposure and again after exposure | 6 | 6 hours | 2,000 | cardiac sensitization to exogenous epinephrine (1/6) | Ibid |
| Liver damage | rat | | 20 | 7 hr/day 5 day/wk 30 days | 5,000 | slight liver damage | Clayton, 1962 |
| | rat | | 12 | 7 hr/day 5 day/wk 30 days | 5,000 | abnormal weight gain, 3 rats pale livers | Clayton, 1966 |
| Thyroid | monkey | | 4 | 2 weeks | 2,000 | enlarged thyroid (4/4) | Carter et al., 1970 |
| Psychomotor ability | human | inhalation | 2 | 0.5 to 1 hour | 2,500 | loss of concentration, drowsiness, dizziness (reversible upon cessation of exposure) | Stopps and McLaughlin, 1967 |

TABLE 5-12. NO OBSERVED ADVERSE EFFECT LEVEL

| Criteria | Species | Mode of Treatment | No. of Subjects Deaths/Total | Duration of Exposure | Conc. (ppm) | Response | Reference |
|---|---|---|---|---|---|---|---|
| Cardiac Sensitization | beagle dog | treadmill inhalation chamber | 0/8 0/4 | 16 minutes | 10,000 20,000 | no effect on cardiac rhythm | Mullin et al., 1971 |
| | dog | fright (electric shock or noise) and fluorocarbon inhalation | 0/12 | 5 minutes | 12,000 | no effect on cardiac rhythm | Haskell Laboratory, 1969 |
| Liver and other organs | rat | chronic inhalation | 0/20 | 6-hr/day 5 day/wk 90 days,1 year | 20,000 | no effect on liver or other organs | Schneider, 1982 (90-day data) |
| | | subacute inhalation | 0/20 | 7-hr/day 30 days | 2000-3000 | Pathology Normal | Clayton, 1966 |
| | | subacute inhalation | 0/5 | 3.5-hr/day 20 days | 25,000 | no change, liver or other organs | Clayton, 1966 |
| | guinea pig | subacute inhalation | 0/3 | 3.5-hr/day x20 days | 25,000 | no change, liver or other organs | Clayton, 1966 |
| | dog | subacute inhalation | 0/2 | 3.5-hr/day x20 days | 12,500 | liver, other organs, all normal | Clayton, 1966 |
| Clinical Examination | human | inhalation | 0/50 | 3-yrs. | 700 (46-5,000) | no effects | Imbus & Adkins, 1972 |
| Psychomotor Effects | human | inhalation | 0/2 | 2 3/4 hrs. | 1,500 | no effect manual testing card sorting | Stopps & McLaughlin, 1967 |
| | human | inhalation | 0/4 | 6 hrs/day 5 days | 1,000 | no effect clinical testing psychomotor performance subjective impression | Reinhardt, 1971 |

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# 6. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

In March 1978, both the U.S. Environmental Protection Agency and the Food and Drug Administration banned fully-halogenated chlorofluorocarbons as propellants in nonessential aerosol uses (Fed. Reg., 1978). It should be noted that while this ban applied to CFC-113 used as the propellant or as a component of the propellant in nonaerosol products, the ban does not cover use of CFC-113 as a solvent or active ingredient in aerosol formulations, nor does it apply to the main uses of CFC-113 in nonaerosol applications.

The concentration of CFC-113 in the workplace to which nearly all workers may be repeatedly exposed without adverse effect is 1,000 ppm (7,700 $mg/m^3$). This Threshold Limit Value (TLV®) has been established for CFC-113 by the American Conference of Governmental and Industrial Hygienists (ACGIH, 1981). This value was recommended as a limit of good hygiene control for vapors of low toxicity (ACGIH, 1971).

References are cited in Section 5.4, Chapter 5.



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